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Scott Meissner *

Posted Date: 13 May 2025

doi: 10.20944/preprints202505.0957.v1

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Review

Yet Even More Proposed Tests of the Soliton-AP Model: Still No Compelling Evidence for It After Twenty Years of a Metaphysical Approach

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Abstract: It has been twenty years since the soliton-action potential (AP) model was introduced, so an evaluation of this model and its status is presented. It will be noted that there is, still, no compelling evidence for this model's assumption that a major lipid phase transition occurs during APs. Concerning the views of anaesthetic actions, changes in capacitance, alterations in membrane width and optical features during AP which the soliton-AP model presents, it is noted that alternative views account for these features in a manner consistent with the modern electrophysiological AP model. It is also noted that the soliton-AP model's proposed means to account for the electrical features of the AP has yet to be shown to operate. Comments will be presented on the recent proposals that an AP has a wavelength, and for a new mechanical synapse hypothesis. It will be suggested that claims for the soliton-AP model to be adiabatic, and for AP passage upon collision, may imply that this model violates the law of conservation of energy. And the claim that APs do not generate net heat will be questioned and refuted by examination of published data. Thus twenty years after its introduction, no clear support is found for the soliton-AP model. Of concern is the apparent abandonment of the scientific method and its standards of evidence by some advocates of the soliton-AP model, as seen in the discounting of evidence judged to be inconsistent with their model. Rather a metaphysical view is offered in which the soliton-AP model is argued to be valid based merely on its alleged association with certain principles and laws. It is suggested that the scientific method's approach of judging a model against data is the appropriate standard of evidence and should be used to evaluate the soliton-AP model.

Keywords: action potential; soliton; scientific method; metaphysics; lipids; membranes

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Acknowledgments.

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"*The method of science, as stodgy and grumpy as it may seem, is far more important than the findings of science.*" Carl Sagan (1997, pg. 26).

Introduction

Scientists typically welcome new and original thinking. The opportunity to find new ways to account for phenomena in a manner which better incorporates both old and new data generally is intellectually interesting. New proposals typically have their assumptions and predictions tested, and if the results of those tests support the new proposed model, and if it can be shown to account for other related findings obtained in the past, then often confidence in the new model grows, and more people may come to accept and use it as a framework for their thinking.

However, there is one relatively new proposed model which, while it certainly displays some interesting and original thinking, has not managed to gain broad acceptance; this is the soliton-action potential (AP) model (Heimburg et al., 2005; Appali et al., 2012). This model was proposed as an alternative to what here will be called the electrophysiological AP model, which includes many revisions and alterations of the original Hodgkin-Huxley AP model (Hodgkin et al., 1952a) from which it is derived. This soliton-AP model attempts to account for the features of an AP by presenting it as physical wave, based on a major lipid phase transition happening in the plasma membrane of the excitable cell during the AP. The soliton-AP model was first presented about twenty years ago (Heimburg et al., 2005), and since that time there have been dozens of articles published which expand on the original presentation and advocate for this soliton-AP model (for a list of specific articles see Meissner, 2022). Recently one of the advocates of this soliton-AP model has published a new review of this model (Heimburg, 2025) which presents some new proposals. This article is largely a response to some of the issues raised by Heimburg (2025), and to aspects of the soliton-AP model in general.

One interesting facet of the soliton-AP model is how it seemingly alters cause-and-effect relationships compared to the standard electrophysiological AP model. Under the electrophysiological AP model the electrical field changes which occur during an AP are considered to induce secondary physical effects (El Hady et al., 2015). Thus a change in transmembrane voltage causes physical changes. While in the soliton-AP model a physical change, based on a presumed lipid phase transition as a molecular mechanism, is suggested to be the cause of the electrical features seen during an AP (Heimburg et al., 2005, 2006). Thus the advocates for the soliton-AP model would suggest that a physical change is producing a secondary electrical effect. In the topics considered below, we will see that this apparent inversion of cause-and-effect between these two models comes up several times.

One purpose of this article is to review some of the proposals and claims which Heimburg (2025) presents in his recent article about the soliton-AP model. One issue which arises concerning the soliton-AP model is that often many of its advocates do not question whether their assumption that a lipid phase transition happens during an AP is valid or not. Instead, it will be argued that they often go right past that assumption and then propose other inferences which they claim, either directly or indirectly, should support the original assumption. Thus no direct evidence is offered, and instead we get indirect arguments. But since even Heimburg (2007, pg. 311) notes that this manner of argument should not be "... taken as final proof..." it seems appropriate to consider some of the these indirect arguments being made by Heimburg (2025), and to examine the alternative explanations for some of them in turn. In some cases these alternative explanations are in need of further study, but in several cases they are quite well supported by evidence, and often these alternatives are seen as being consistent with the electrophysiological AP model. Therefore, given that we have no direct evidence of an actual lipid phase transition happening during an AP, the scientific method suggests that reasonable alternatives should be examined in an open manner. If the reader compares what follows in this article on these topics to what is often given in articles by some of the advocates for

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the soliton-AP model (see for instance Heimburg, 2025), they may well note that these alternatives are often given only passing mention, or are entirely ignored.

Another purpose of this article is to present, especially for those who are encountering the soliton-AP model for the first time, some sense of why this model is not currently widely accepted by many scientists. The intent in previous reviews of the soliton-AP model (Meissner, 2018, 2022) has been to note the sorts of tests, and the types of findings from such tests, which the good people who advocate for this soliton-AP model would need to present if they wish to make an evidence-based argument for their model. This will be continued here in this article where several new tests will be proposed. This is done in the spirit of the scientific method, and if the advocates for the soliton-AP model are able to obtain the needed evidence to make a convincing evidence-based argument for their model, then the author of this review, as a dutiful philosopher, will be very interested in examining such findings. If clear, compelling, and reproducible results in support of the soliton-AP model are presented, then under the scientific method this model may well gain acceptance and be taken up with growing confidence and interest. Of course, if no such evidence is presented, or if what is presented turns out to be flawed, then the soliton-AP model may remain as it is now: an interesting conjecture but not strongly accepted due to the lack of supporting evidence. Thus the lack of convincing evidence will be argued to be the current state in which we find this soliton-AP model at this time, and a major reason for its lack of acceptance.

Finally, another purpose of this article is to note, as has been described previously (Meissner, 2022), and to further illustrate, how some of the good people who advocate for the soliton-AP model are often not using the scientific method and its standard of evidence. Instead the arguments presented by some of the advocates of the soliton-AP model often take a metaphysical approach; they presume that their model is so directly and tightly mandated by laws and principles in which we have strong confidence that their proposed soliton-AP model must also be worthy of strong confidence. This confidence is displayed by their using their model to judge which data are to be seen as correct, which is the exact opposite of the scientific method where a new model would be judged by the data. Examples of this use of an apparent new standard of evidence will be described with regard to several of the issues covered in this article. The argument will be made that those proponents of the soliton-AP model who thus abandon the scientific method's standards of evidence for a new metaphysical standard of evidence are, in effect, no longer behaving as scientists, and are instead acting as natural philosophers.

Whither the Phase Transition?

It has been stated (Heimburg, 2025) that a central feature of the soliton-AP model is its assumption that a major lipid phase transition is happening as its basis for the AP. In his recent article, Heimburg (2025) cites earlier work from his group about this assumption, such as Græsbøll et al. (2014, pg. 2144) where it is stated; "Such melting transitions in fact have been found for a number of biomembranes (30)." It should be noted that the item cited here (30) is Heimburg's own 2007 text, which largely explores artificial lipid bilayers, and not biomembranes as found in actual living cells. Heimburg (2025), in his recent article, also cites his own 2007 text on this matter of lipid phase transitions (Heimburg, 2007, pg. 311) and notes several suggestive features associated with lipid phase transitions, and then states: "The data mentioned above should be taken as a hint toward the existence of transitions during the nerve pulse but not as a final proof." And later on Heimburg (2007, pg. 320) states: "...we have no direct data on the melting of nerve axon membranes..." However Heimburg (2007, pg. 285) also states; "Little is known about the relaxation times of the cooperative processes in biomembranes. However, let us be courageous and assume that the linear relation between heat capacity and relaxation times is the same for biomembranes as it is for model membranes." By his reference here to "model membranes" Heimburg is apparently referring to simple artificial phosopholipid bilayers, and not to actual biological membranes as found in living cells. From these statements it seems clear that the presence of lipid phase transitions in biological membranes is a major assumption of the soliton-AP model, but not yet an established fact. Given this

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key assumption, it seems reasonable, as noted previously (Meissner 2018), to raise questions as to whether or not something like a liquid-crystalline to gel phase transition actually happens during an AP in biological membranes, as the soliton-AP model assumes. Typically in science such assumptions are subjected to testing, and then only accepted when verified by direct evidence. We will see that this is not the case for some of the advocates of the soliton-AP model, who adopt a different standard of evidence in this matter which is evident in that they accept the soliton-AP model and its various assumptions and predictions without always having obtained confirming evidence.

It has also been noted that for the soliton-AP model to account for certain AP features, such as AP velocity, the phase transition that is assumed to be happening during an AP would need to have a sufficient enthalpy (i.e., heat) of transition, so that when this enthalpy value is put into the equations which the advocates for the soliton-AP model use they can get estimates of AP features, including its velocity, similar to those observed in actual cells (Meissner, 2022). So not just any lipid phase transition with any enthalpy of transition would be acceptable here. Generally the assumption is made that the enthalpy of the presumed lipid phase transition proposed to be happening during an AP would be about 35 kJ/mol, this being the value seen for DPPC lipid bilayers undergoing a liquid-crystalline to gel transition (Heimburg et al., 2006; Mosgaard et al., 2015). It should be noted that not all lipid phase transitions have such a large enthalpy of transition. For instance, a liquid disordered (Ld) to liquid ordered (Lo) phase transition is reported by Almeida (2011) to have a much lower energy change compared to that of some other phase transitions. All this naturally leads to questions as to whether any sort of lipid phase transition(s) happen normally in the plasma membranes of eukaryotic cells, and most especially in excitable cells such as neurons, and if so, can the enthalpy of that phase transition be measured so that the soliton-AP model equations can be used to then estimate the resulting soliton features which would be expected? So let us look at some studies on whether or not such lipid phase transitions are detected in either the plasma membrane of cells, or in phospholipid bilayers with compositions which mimic somewhat that of the plasma membrane.

As has been noted previously (Meissner, 2022), due in part to the high cholesterol content of the plasma membrane of many cells, it may be questioned whether a lipid phase transition can happen in the plasma membrane under normal physiological conditions (Shaw et al., 2021). One study of interest here is from the lab group of Prof. Heimburg (Peters et al., 2017), which used differential scanning calorimetry (DSC) and found that in DMPC vesicles, when given a cholesterol content similar to that often seen in neuron plasma membrane, there was, by DSC, no phase transition detected, meaning that no heat of transition was detected. This finding implies that since there is no heat of transition detected, then, in the presence of cholesterol at the level used, perhaps no lipid phase transition is happening and so no soliton can be produced? It should also be noted that this study also used neutron scattering to follow any lipid phase changes as well, and they state about results obtained using this method the following (Peters et al. 2017, pg. 3): “Similar to the DSC data the sterols wash out the effect of the phase transition, which is no longer visible for the cholesterol concentrations of the neutron scattering experiments at any applied pressure.” This finding of no detectable phase transition in the presence of a certain content of cholesterol has been noted before (Steim et al., 1969; Meissner, 2022). Thus, here are two methods used by Peters et al. (2017), DSC and neutron scattering, which failed to detect a clear lipid phase transition when cholesterol was present in these DMPC vesicles, which is to say at a cholesterol content similar to that often seen in the plasma membrane of neurons. As noted above, if the enthalpy of phase transition can not be measured, then the soliton-AP model would have no value to input into its equations, and so no estimate could be made of what, if any, soliton features would occur. Indeed, without an actual lipid phase transition being detected here, one could argue that soliton production should not occur under these conditions. Oddly, in discussing their findings Peters et al. (2017, pg. 7) suggests that this “... disappearance of the enthalpy of transition might be an artifact of this technique...” a claim which would seem to need some examination. Are they suggesting that we should assume that a lipid phase transition is happening which cannot be detected? What would be the basis for such an assumption? Obviously, the failure of a lipid phase transition to be detected would suggest there may be compositions of lipid

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bilayers, and by extension of biological membranes, for which lipid phase transitions of high enthalpy changes just may not occur, as has been noted earlier (Meissner, 2018, 2022). After all, it has been noted that high cholesterol content in lipid bilayers can inhibit lipid phase transitions and the formation of lipid pores (Bennett et al., 2009).

So if there is no lipid phase transition detected under these conditions, that would cast doubt on this major assumption of the soliton-AP model, that during an AP a major lipid phase transition happens, and deny us a definite value of its enthalpy of transition for use its calculations of its presumed soliton features. We may then ask, is the reason that Peters et al. (2017) refer to these findings as an "artifact" simply to try to find a way to view their results in a manner which permits the soliton-AP model to be viable? If so, that would show how under their philosophical approach, some of the good people who advocate for the soliton-AP model are willing to fit the data to their model in a rather extreme manner. While Heimburg may view such an approach as being "courageous" (Heimburg, 2007, pg. 285), it also seems to require that we should accept something, in this case that a lipid phase transition is happening, even though no direct evidence of its occurrence exists. This suggests a very different standard of evidence is being used here compared to that used under the scientific method, as suggested earlier (Meissner, 2022).

Another means to look for evidence of a lipid phase transition in a eukaryotic plasma membrane would be to look at the effects of such a lipid phase transition on the capacitance of the membrane. The liquid-crystalline lipid phase of a DPPC bilayer is known to be thinner, and so should have a higher capacitance, compared to the thicker gel phase (Heimburg, 1998). Thus if an AP is based on a soliton, which in turn proposes a major liquid-crystalline to gel phase transition as its molecular mechanism, then, as Heimburg (2025, pg 9) notes: "A soliton will therefore transiently reduce the capacitance of the membrane." Note that this implies that a sudden shift to a lower capacitance would occur during an AP. Heimburg (2025; pg. 8) also claims that such a lipid transition would occur at about 10-15°C below normal body temperatures. Thus, if a plasma membrane's capacitance is monitored while altering the temperature of the system, then a major shift in the lipid phase state should show up as a sudden shift in the capacitance seen. Such a use of capacitance shifts to monitor lipid phase changes across a range of temperatures has been demonstrated using egg lecithin bilayers (Antonov et al., 2003). While such bilayers are not biological membranes (as they lack proteins and other features), this does at least confirm that this approach has a reasonable potential to detect sudden lipid phase change-induced capacitative shifts. The question then is whether in an actual biological membrane evidence for a lipid phase transition can be found if a section of plasma membrane was taken across various temperatures and its capacitance monitored. Recently Bassetto et al. (2023) were able to carry out such an experiment. They used frog oocytes which have a cortical pigment which could absorb light and so allows for local heating, and then while raising the local temperature in stages they were able to monitor the capacitance of a section of membrane across a temperatures span of 0-50°C. Bassetto et al. (2023, see their Fig. 1D) found that the capacitance of the membrane rose in a clearly linear relationship with rise in temperature. They report no sign of any distinct sudden change in capacitance across the temperature range tested. This finding may question the assertion that the advocates of the soliton-AP model often make that major lipid phase transitions are seen in all biological membranes, and so raises more doubt as to whether their soliton-AP model truly is viable. Thus, here is a third method which seems to indicate that, unlike in simple homogeneous phospholipid bilayers, biological membranes may not exhibit large lipid phase transitions. It should be noted that frog oocyte plasma membranes are not normally excitable. However Shapiro et al. (2012) found that with the introduction and expression of the genes needed for the Na^+ and K^+ voltage-gated channels, a frog oocyte then does display APs. It would therefore be interesting to repeat Bassetto et al. (2023)'s work to examine the capacitance of the plasma membrane across this same range of temperatures using this sort of genetically transformed frog oocyte to see if in an excitable cell membrane major lipid phase changes are indicated via their influence on capacitance compared to the results presented for a nonexcitable membrane.

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Another method that can be used to detect large scale lipid phase transitions is that of Raman spectroscopy. This method has been used to examine the influence of protein/lipid interactions on lipid phase changes in phosopholipid bilayers (Heimburg et al., 1991). It should also be noted that heating of neurons by infrared treatment has been found, via Raman spectroscopy, to result in detectable lipid rearrangements (Adams et al., 2022), suggesting that this method can detect lipid rearrangements in native membranes when such changes happen. Three studies have applied this method to neurons known to be able to fire APs, and in each case no clear evidence of a distinct lipid phase transition was reported (Pézolet et al., 1985; Savoie et al., 1986; and Lee et al., 2017). Pérolet et al. (1985, pg. 367) states... "The temperature dependence of these bands does not reveal any thermotropic phase transition between 0 and 40°C." The second study used Raman spectroscopy to look for any changes in arrangement of lipids during the actual passage of an AP, and they note (Savoie et al., 1986, pg. 329) "Our results show that if there are any spectral changes during nerve excitation, these are less than 0.5% for both the phospholipid and carotenoid bands." While the study by Lee et al. (2017) followed the signal bands appropriate for a functional group associated with lipid acyl chains (the CH_2 group in acyl chains vibrates at 2850 cm^{-1}), as well as the vibration of the CH_3 groups (at 2930 cm^{-1}) often found in the side groups of amino acids in proteins. Lee et al. (2017) found that the signal at 2930 cm^{-1} (that of the amino acids) did shift during AP passage, but the signal at 2850 cm^{-1} (that of the lipid acyl groups) did not shift during AP passage. This implies that protein conformation changes were happening during the AP, and Lee et al. (2017) found good evidence that a major part of the signal they detected could be attributed to shifts in the voltage-gated sodium ion channels during the AP. This Raman spectroscopy study thus suggests that protein conformation changes occur during AP, but found no clear evidence of any major lipid phase transition happening during APs.

What should we conclude

Thus we have here four methods (DSC, neutron scattering, electrophysiological monitoring of membrane capacitance, and Raman spectroscopy) all of which, in the above noted studies, gave negative reports with regard to whether a lipid phase transition can occur in a bilayer with a high cholesterol content, similar to that seen in neuronal plasma membranes, or to the assumption that in biological membranes a major lipid phase transition commonly happens. A review of lipid phase transitions, as examined via many different approaches (Olfield et al., 1972), also noted many cases, in both phospholipid bilayers of certain compositions and in biological membranes, where lipid phase transitions could not be detected by a wide range of methods. Thus, in the absence of any new evidence, what we have here would seem to force us to the conclusion that the assumption which the soliton-AP model makes, that there are lipid phase transitions happening during an AP, is not supported by current evidence. How the good people who advocate for the soliton-AP model respond to this sort of evidence is of interest.

It has already been noted above that the Peters et al. (2017) study claimed that this failure to find evidence of a lipid phase transition in phospholipid systems with a high cholesterol content was, they suggest, due to some sort of "artifact" when using DSC. With regard to the use of Raman spectroscopy, there is a posted preprint which presents an entirely reworked analysis of the Lee et al. (2017) data, and presents the conclusion that the lipids in the system must have been undergoing some sort of thermotropic transition, another way of referring to a lipid phase transition (Shrivastava et al., 2020). In effect, where the analysis done by Lee et al. (2017) found a change in protein conformations but no evidence for a lipid phase transition, the Shrivastava et al. (2020) preprint suggests that those same data indicate that a lipid phase transition was happening based on changes in signals which the Lee et al. (2017) article said were specific to the proteins alone. Thus, the response to some of this negative information on lipid phase transitions by these advocates of the soliton-AP model is to either call the results an artifact, or claim that the findings mean something other than what the original study concluded. Implying, again, that these advocates for the soliton-AP model are using a different standard of evidence. In this case that their soliton-AP model must be viewed as

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valid and the data must be made to fit that model, or be denied if found to be inconsistent with their model.

The point remains that if during an AP no lipid phase transition has yet been detected, and therefore no estimate of the enthalpy of phase transition has been made, then there is no specific value of enthalpy to be put into the equations which the soliton-AP model uses. So in the absence of an ability to make use of an enthalpy value which was measured from actual excitable membranes, the value actually used in estimates made via the soliton-AP model is often one which is needed in order to produce the desired features in the hypothetical soliton. Indeed both the Heimburg et al. (2006) and Mosgaard et al. (2015) articles make use of an enthalpy of the phase transition for a DPPC bilyaer, 35 kJ/mol, in estimating the features of a soliton wave that might occur. Thus, on top of assuming that a lipid phase transition occurs during an AP, these advocates for the soliton-AP model also assume a value for the enthalpy of that undetected phase transition to input into their equations. And so, assumption is piled on top of assumption.

However, the important point to note is that since the introduction of the soliton-AP model, 20 years ago (Heimburg et al., 2005), the good people who advocate for this model have not, even yet, found clear positive direct evidence that compels us to take up the view that any sort of major lipid phase transition happening during an AP; neither in artificial phospholipid bilayers systems with a composition which closely matches that of the neuron plasma membrane, nor in actual plasma membranes of neurons. Thus they present no evidence in support of this basic assumption of their model, as noted earlier (Meissner, 2018). Why they have not focused their attention on this critical assumption of their model might be explained by their utter faith and acceptance that thermodynamics and perhaps other principles or laws somehow mandates, in their view, that such lipid phase transitions must occur? Thus any evidence, including this negative evidence concerning lipid phase transitions during an AP, which questions their model is not of interest to these good people. They feel convinced that their model is correct, and so any disconfirming evidence encountered must therefore be rejected. It seems that, in their view, their model should be able to judge and select which set of evidence is to be accepted; the model judges the data. So it would seem that many of these good people are using a very different standard of evidence compared to the scientific method, where a model would be judged by new data. Therefore, as argued previously (Meissner, 2022), many of the advocates of the soliton-AP model have abandoned use of the scientific method. Their arguments are made largely from faith in their model, and not from actual evidence.

Concerning the Anaesthetic Argument

In his recent article, Heimburg (2025) repeats the suggestion that the soliton-AP model might be a means to account for the observation that some anaesthetics are able to inhibit AP firings in neurons. However, this argument is largely based on work done on simple homogeneous phospholipid bilayers. It is noted that application of pressure can sometimes inhibit the effects of some anaesthetics, and the suggestion is made that entry of these molecules into lipid bilayers often increases the local bilayer volume, and this would be reversed by the application of pressure. In essence these good people are arguing that anaesthetic effects result from an inhibition of their model's assumed lipid phase transition, which they propose to be the basis for an action potential (Trudell, 1977; Seeger et al., 2007; Blicher et al., 2009; Græsbøll et,al., 2014; Wang et al., 2018). There are some difficulties with this proposal which deserve consideration.

One consideration is that it is rather difficult to show that a given anaesthetic treatment can inhibit a lipid phase change in the plasma membrane of a neuron when, as note previously, there is no clear evidence that such a lipid phase change actually occurs during an AP. Thus we are in the interesting realm of considering an inhibition of something which has not been detected; truly a difficult argument. Further, in his recent article (Heimburg, 2025) it is implied that this proposed anaesthetic effect should be seen as a reason for accepting the soliton-AP model as it is claimed to show the predictive power of this soliton-AP model. In essence, this suggestion is proposing that an inference, which is dependent on an unconfirmed assumption, should be taken all by itself as

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evidence in support of the assumption upon which it depends. Thus, because of this prediction we are encouraged to accept that the soliton-AP model's assumption that a lipid phase transition happens during an AP is valid. This, of course, is classical circular reasoning. Naturally, IF solid evidence for a lipid phase transition during an AP in the plasma membrane of neurons and other excitable cells was found, then it might be possible to test if anaesthetic application could inhibit it. But in the current absence of such evidence, a mere inference is not evidence for an assumption on which it depends, and is essentially untestable. Thus there is a major problem with the logic of the argument being presented by the advocates of the soliton-AP model in this case.

Another consideration here is that there is much debate on whether anaesthetics act just on the lipid structural arrangements in biological membranes, or whether they might act directly on protein structures as well. One interesting article (Layne, 1984) suggests that a proposed soliton, which would move along the alpha helical domains of a protein, may be blocked by the presence of anaesthetics which would alter the protein structure and prevent this proposed soliton-within-protein phenomenon. Thus Layne (1984) suggests that anaesthetics may act directly on protein structure. Prof. Heimburg (2025) in presenting his arguments for anaesthetic affects on lipid phase transitions cites the work of Johnson et al. (1950) as evidence in support of his case. However, this reference is rather odd as what Johnson et al. (1950) examined was the anaesthetic effects on a soluble fluorescent protein. In a later review article, Johnson (1955) notes that this protein had been isolated and the inhibition of its light production by anaesthesia observed *in vitro* in the complete absence of any cell membrane. What Johnson et al. (1950) and Johnson (1955) and others (Nosaka et al., 1988; Duarte-Gómez et al., 2014) note is that in some cases anaesthesia denatures this protein, a process which increases the volume of the protein, and so applied pressure would be expected to counter this anaesthetic effect and restore the protein activity. Thus, our good Prof. Heimburg (2025), by citing Johnson et al. (1950), is citing an article which examined the effects of anaesthesia on cytosolic proteins, and so how Heimburg can offer this as evidence in support of his claim of anaesthetic effects on cell membrane lipid organization is unclear. Citing an article which studies anaesthetic effects on a protein in support of proposed anaesthetic effects on lipid arrangements does not seem to be a very logical connection.

Thus, while the advocates for the soliton-AP model suggest that anaesthetic effects are due to an inhibition of an, as of yet, unobserved lipid phase transition during APs, others note that anaesthetics, being small hydrophobic or amphipathic molecules, are able to enter the hydrophobic regions of proteins and so may act broadly on protein structures (Ueda, 2001; Sarkar et al., 2010), which would be an explanation totally independent of any effects on membrane lipid structure. Indeed, Ueda (2001; pg. 20), while arguing that the action of the anaesthetics is on proteins, notes that the lipid solubility of these anesthetics often creates confusion; "The lipid theories are often misinterpreted to mean that the anaesthetic action site is lipid membranes." This action of anaesthetics on protein structure seems to be an aspect of anaesthetic effects which Prof. Heimburg (2025) fails to note in his recent article. But the action of anesthetics on proteins has been an major focus of study by many researchers over the years.

Thus inhibition of action potentials by anaesthetics is indicated by findings that these compounds interact with, and alter the activity of, a variety of proteins; including the voltage-gated sodium ion channel (Herold et al., 2017; Körner et al., 2022), the proteins involved in synaptic vesicle fusion needed for neurotransmitter release (van Swinderen et al., 2001; Das, 2020), nicotinic acetylcholine receptors at synapses (Forman et al., 2015), and the presynaptic protein syntaxin 1A (Hawasli et al., 2004). Indeed in examining ethanol effects on GABA receptors in mice, Tapia et al. (1998; pg. 243) concluded; "In summary our data indicates that although ethanol affects the glycine receptors in spinal neurons it does not change the macroscopic properties of the lipid phase." A conclusion about anaesthetic effects which Herold et al. (2017, pg. 617) also reached; "These results suggest that anaesthetics directly interact with membrane proteins without altering lipid blayer properties at clinically relevant concentrations." The work of Roth et al. (1976) report that the ability of pressure treatments to reverse anaesthetic effects is often variable with temperature and with the

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type of drug applied, and they suggest that the diversity of action of these drugs and of any pressure treatments may be due to the different proteins involved. Thus a good number of workers suggest that the action of anaesthetics is mainly on protein structure, and that any influences on the lipids might have indirect effects then on membrane proteins (Rajaram et al., 1999).

Since anaesthetics are generally rather hydrophobic, they naturally partition into the hydrophobic region of a biological membrane or lipid bilayers. If enough enters, this may result in an alteration of the thickness of a phospholipid bilayer (Moldovan et al., 2014), as well as producing a effectively higher concentration of the anaesthetic within the bilayer's hydrophobic region. Thus, in biological membranes, this may present the hydrophobic sections of membrane spanning proteins to higher local anaesthetic concentrations, which might then enhance their interaction with the these proteins' hydrophobic regions (Herold et al., 2017). Or, the altered membrane thickness may interact with membrane spanning proteins and alter the protein activities. Thus, there are arguments made that some anaesthetic effects on membrane proteins may be due to effects of the anaesthetics on the membrane lipid thickness or other properties (Butterworth et al., 1990; Rehberg et al., 1995; Goksu et al., 2009; Drexler et al., 2011; Tsuchiya et al., 2013; Jerusalem et al., 2019), but the ultimate action may well be on protein activities.

What should we conclude

While there is a debate over anaesthetic modes of action, the advocates for the soliton-AP model often ignore evidence for anaesthetic actions on proteins and focus mostly on their assumption that anaesthetics inhibit lipid phase changes in biological membranes. If there was evidence for such lipid phase changes happening in association with APs, and then, if anaesthetics were actually shown to inhibit such lipid phase changes in such biological membranes, that might be a solid argument in support of their soliton-AP model. But in the absence of such evidence this becomes yet another example of the way that the advocates for the soliton-AP model are not making an argument from evidence. They are convinced that their model is "correct" (Andersen et al., 2009, pg. 107) as they claim it is, somehow, supported by thermodynamics or some other major laws or principles. Thus they are making an argument based on faith, not on evidence, and are stating what they believe is implied by their soliton-AP model. Their belief is so great that it often seems the lack of evidence in support of this view concerns them not at all. On the other hand we have clear evidence that some protein activities which are needed for AP actions can be inhibited by anaesthetics, which is consistent with the existing electrophysiological AP model.

About Capacitance

The capacitance of biological systems is of interest, especially of biological membranes, and can be measured by common methods (Schoenberg et al., 1975; Neher et al., 1982; Lindau et al., 1988; Gentet et al., 2000; Bretschneider et al., 2006). The influence of capacitance is also noted in studies which examine the more complex trait of impedance (Cole, 1941; McAdams et al., 1995). Recall Heimburg's (2025, pg 9) statement that: "A soliton will therefore transiently reduce the capacitance of the membrane." In fact, it has been reported that during an AP there is a transient rise in capacitance seen in the plasma membrane of excitable cells (Takashima, 1976; Crotty et al., 2007; Bezanilla, 2018), and this has led to some studies which incorporate capacitance into empirical models that attempt to describe APs (Fernandez et al., 1983; Howell et al., 2015; Iravanian et al., 2019). This is yet another new modification to our understanding of the AP, and is in contrast to an earlier assumption that capacitance did not shift significantly during an AP (Huxley, 2002). This shows, yet again, that we need to continuously test our assumptions. Indeed, the changes in capacitance of the plasma membrane in some cells has been reported to be voltage-dependent (Zimmermann et al., 2008; Zhang et al., 2018), and in one interesting study it was found to shift regularly following a circadian rhythm across the day (Severin et al., 2024). Two possibilities, which are not necessarily mutually exclusive, have been proposed to account for the capacitance shifts during APs; changes associated

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with the membrane proteins, or changes associated with the lipid arrangements during an AP. Next each of these will be considered.

Capacitance is related to surface features, and proteins being dipolar molecules with a high surface area as well as being highly flexibility can contribute significantly to capacitance. So it is not surprising that even soluble proteins can contribute capacitance to a system even in the absence of membranes (Lund et al., 2013; Božič et al., 2021; Rahimi et al., 2022). Indeed, there is ongoing work on the use of soluble soybean proteins as a basis for capacitative storage batteries (Ferrero et al., 2015). Thus, membrane proteins can contribute to the capacitance of a biological membrane, and anything which alters the conformation of these proteins can alter their contribution to capacitance (Bassetto et al., 2023). This can be due to large protein conformational changes which either alter the surface area of the proteins or expose new dipole or charged areas (Sivasankar et al., 1998; Zimmermann et al., 2008; Bae et al., 2015), or via the binding of ligands which may cover protein regions altering their contributions to capacitance (Burtscher et al., 2020), or it can be due to the movement of small domains of the proteins which carry charged side groups producing a capacitative shift at the surface of the membrane. This last item is seen in the shift of voltage-sensing domains of many proteins including protein-based ion channels (Oliver et al., 1999; Sfondouris et al., 2008; Gleitsman et al., 2009; Zhang et al., 2018; Burtscher et al., 2020; Santos-Sacchi et al., 2022), and this is sometimes referred to as a "gating current" (Bekkers et al., 1990; Kim et al., 2016a; Bezanilla, 2018; Ruíz-Fernández et al., 2021). This can also be viewed as a shift in the protein's dielectric value in association with its conformational changes (Li et al., 2013). This capacitance-related gating current is often much smaller than the ionic currents which cross the membrane during an AP (Bezanilla, 2018), but their contribution to the capacitance can alter the time constant (i.e., the RC value) of the system and so can influence certain features of the AP. Thus, with the presence of membrane proteins with voltage-sensing domains able to shift in response to changes in membrane potential which occur during an AP, it would be expected that there should be alteration of the conformation of such protein domains and this would contribute to shifts in the membrane capacitance in a voltage-dependent manner. Indeed, the use of such voltage-sensing domains in protein-based ion channels is central to the electrophysiological AP model, and so is yet another alteration to the earlier Hodgkin-Huxley AP model (Hodgkin et al., 1952a) back when this mechanism was still merely hypothetical.

The other class of molecules in biological membranes which are dipoles are, of course, the lipids. Thus lipids can display voltage-dependent molecular shifts which may alter exposed charged, or partially charged, residues and so can contribute to changes in the capacitance of lipid bilayers (Alvarez et al., 1978). However, Alvarez et al. (1978) notes that the contribution of lipids to voltage-dependent capacitance shifts in a phospholipid bilayer was just a small fraction of the capacitance changes reported being due to proteins in biological membranes. One study (Schoch et al., 1979), using asymmetric lipid bilayers found that the capacitance in this system was indeed associated with surface potential changes, and that across a 100 mV bilayer potential shift the capacitance could be altered by up to 0.06%. Ohki (1969), working with phosphatidyl choline and phosphatidyl serine bilayers, found that over an imposed transbilayer potential change of 200 mV, the bilayer capacitance shifted by just 0.01 $\mu F/cm^2$ relative to a base bilayer capacitance of 0.5 $\mu F/cm^2$. Others (Toyama et al., 1991; Velikonja et al., 2016) also note that the voltage-dependent changes in capacitance that can be attributed to lipids are often lower than that reported to be due to proteins in biological membranes. Thus while lipids are dipole molecules, and do respond to voltage shifts, their influence on changes in capacitance of a bilayer, or of a biological membrane, is suggested by these studies to be much lower than that contributed by the membrane proteins.

Thus the electrophysiological AP model places capacitance changes during the AP as another side effect of the electrical potential changes that happen during the AP, and most of this can be attributed to the sensitivity of protein conformations to the transmembrane voltage, with the lipids perhaps contributing a small amount to the observed voltage-dependent capacitative shift as well. The soliton-AP model takes a different view.

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Under the soliton-AP model there is the assumption of something like a liquid-crystalline to gel phase transition in the membrane happening during an AP. This occurs as a physical wave, and this physical wave is suggested to have electrical effects. A shift to a gel phase is known to lead to a thickening of a lipid bilayer (White, 1970; Heimburg, 1998; Heimburg, 2012; Mosgaard et al., 2015; Zecchi et al., 2017), and such thickening was found to lower the capacitance of the bilayer in some settings (Antonov et al., 2003; Heimburg, 2012), as also noted recently by Heimburg (2025). Thus, if a lipid phase change of this sort is indeed happening during an AP, which is one of the major assumptions of the soliton-AP model, that would be expected to result in a lowering of the capacitance of the system due to the gel phase being thicker than the liquid-crystalline phase. However, this is the exact opposite of what is known to happen during an AP, in that, as noted above, during an AP there is a small but real rise in capacitance seen. One way that a liquid-crystalline/gel phase transition might increase the capacitance would be for the base state to be the gel phase, and the transient shift to be to the liquid-crystalline phase, which is the opposite of what the advocates for the soliton-AP model propose to be happening (Heimburg et al., 2005). Thus, the soliton-AP model does not seem to be able to account for the capacitance changes seen during an AP by any thickening assumed to occur during the hypothetical lipid phase transition they propose as the molecular mechanism for their model.

Thus, as an additional proposal some advocates for the soliton-AP model suggest that it is not the thickness of the membrane that matters, but rather the formation of lipid pores during the proposed phase transition which contributes to the rise in capacitance seen during an AP (Heimburg, 2012; Blicher et al., 2013; Zecchi et al., 2017). This would be similar to what is seen during electroporation, during which lipid pore formation can be associated with a rise in capacitance of the system (Freeman et al., 1994). However, as was noted previously (Meissner, 2018), lipid pores are often nonselective, can allow molecules of various sizes to leave the cell, and so are damaging to cells. By altering the content of their membranes to lower the temperatures at which such phase transitions occur to below those normally encountered, cells avoid the stress that comes with such phase transitions, such as stress from the formation of nonselective pores (Melchior et al., 1976). So here again, the advocates for the soliton-AP model are proposing a mechanism which would seem to need careful examination. Does a lipid phase transition actually happen during AP firing, and if so, is there formation of lipid pores during such an event? As we have no clear evidence for such a lipid phase transition, the matter of what lipid pores might contribute is thus a speculation built upon an, as of yet, unsubstantiated assumption.

Another option, which might be consistent with the soliton-AP model is that its presumed lipid phase transition alters the exposure of charged or partially charged residues in the lipids, mainly in the head group region, which might alter the surface charge density of the lipid area and so contribute to changes in capacitance. However, as noted before (Meissner, 2022), any such phase transition-associated change in surface charge density would be highly dependent on the lipid composition of the system. Recall that some lipids have positively charged head group regions, others negatively charged head groups, and still other lipids are neutral. Bilayers, and so biological membranes, made up of different compositional mixtures could then reasonably be expected to display vastly different capacitative changes when a lipid phase transition occurs due to their compositional differences. Thus, if the advocates for the soliton-AP model wish to strengthen their claim that their presumed lipid phase transition alters the system's surface charge density and so account for capacitative changes seen during an AP, then they might wish to explore this in a system which has a composition of lipids very close to that seen in native plasma membranes and not based on just a non-native and artificial pure phospholipid bilayer?

Another way to test the views put forward by these two models with regard to the changes in capacitance seen during an AP might be the following: The electrophysiological AP model accounts for this capacitance change in a voltage-dependent manner, and the magnitude of these changes will vary with the magnitude of the imposed voltage change. Indeed, even a hyperpolarization of the plasma membrane, to a potential which would not induce an AP firing, would be expected to alter

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the membrane capacitance to some extent. Therefore, the electrophysiological AP model would suggest that this voltage-dependent capacitance should be found to occur outside of actual AP firings. In contrast, the soliton-AP model suggests that the capacitance changes seen during an AP are tied mainly to events associated with some sort of hypothetical lipid phase transition. If there is no lipid phase transition, then there should be no change in capacitance. Thus, the soliton-AP model seems to imply that an all-or-none capacitance shift should be seen. This matter is open to testing, but recall the previously mentioned work by Bassetto et al. (2023), which upon taking a section of biological membrane through a range of temperatures found no indication of any distinct shift in capacitance that might be associated with a lipid phase change, rather a gradual change in capacitance was seen. The advocates for the soliton-AP model might wish to repeat such work, but also consider applying transmembrane voltage shifts, to see if they can detect any step-like shifts in capacitance which would be consistent with their claim of a lipid phase transition happening during APs.

What should we conclude

Taking the above information as a whole, the electrophysiological AP model has a clear and verified mechanism to account for the capacitance changes seen during APs; that of voltage-dependent protein conformation changes producing "gating currents" with voltage-dependent changes in lipid arrangements contributing a smaller amount. In contrast, the soliton-AP model is assuming that an, as of yet, unverified phase transition occurs during AP firings. But a problem here is that a liquid-crystalline to gell lipid phase transition would be expected to thicken the membrane and thus lower the capacitance, as Heimburg (2025) notes, and so that feature of this hypothetical lipid phase transition can not account for the rise in capacitance actually seen during APs. Also, if the argument is that with a phase transition surface charge density changes occur in the lipid areas of a membrane, that would be highly dependent on composition. And so there would be a need for studies of capacitance changes in model membrane systems in which the composition reflects that seen in an excitable system. Or, the good people who advocate for the soliton-AP model may suggest that during this hypothetical lipid phase transition there is lipid pore formation which would then account for this rise in capacitance. Just how the cell is to survive what is effectively electroporation with each and every AP firing under their model is an issue that they have not addressed. In any event, we are presented with two models each proposing ways to account for the rise in capacitance during AP firings, one is well verified and another which is largely speculative at this time. Therefore, the preponderance of the current evidence with regard to a rise in capacitance during an AP seems to support the current electrophysiological AP model.

Concerning Membrane Width and Optical Property Changes

As reviewed previously (Meissner, 2018, 2022), it has long been known that associated with an AP there is a widening of the plasma membrane and that changes in its optical features occur, including changes in its birefringence, light retardation, and ability to scatter light (Cohen, 1973). It is interesting to consider how these features are viewed differently under the electrophyisological AP model versus under the soliton-AP model.

Under the soliton-AP model the thickening of the membrane by about one nanometer during an AP is attributed to something like a liquid-crystalline to gel phase transition happening in the plasma membrane, which this model assumes is the causative basis for an AP and many of its features (Heimburg et al., 2005). An alternative, of course, might be that electrostriction of some sort, operating on a biological membrane, or a lipid bilayer, might also alter either the width of the system or realign the lipid dipolar molecules so as to create changes in its optical features. However, studies have found that application of trans-bilayer potential shifts to a lipid bilayer is unlikely to alter its thickness significantly (Alvarez et al., 1978), nor will it greatly alter the optical properties of a lipid bilayer (Berestovsky et al., 1970). Thus, the soliton-AP model claims to account for the thickening as due to a presumed lipid phase transition, and this they suggest is supported by the finding that DPPC bilayers do show about a one nanometer shift in thickness between a liquid-crystalline and gel set of

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phases (Heimburg, 1998, Heimburg, 2007; Appali et al., 2012). As reviewed earlier (Meissner, 2018), the lipid alignment changes which occur with this phase shift are reported to alter the optical properties of such a bilayer as well (Heimburg, 2007). This claim that these features of an AP can be accounted for by a major lipid phase transition thus makes it all the more necessary for the good people who advocate for the soliton-AP model to show evidence that a phase transition actually occurs during an AP. On this point, we might be wise to recall Heimburg's own statement (2007, pg. 311), where he noted that these sorts of features "... should be taken as a hint toward the existence of transitions during the nerve pulse but not as a final proof," and so to ask, as good scientists should, for actual evidence in support of this major assumption of the soliton-AP model that these AP features result from a major lipid phase transition as its molecular mechanism.

In contrast, the current widely accepted electrophysiological AP model suggests that the observed changes in the width and optical properties during an AP may be the result of the influence of the transmembrane potential changes which happen during the AP acting on the dipole molecules of the membrane, and most especially acting on the membrane proteins. Thus, as noted previously (Meissner, 2018), there are studies which note that voltage-dependent conformational shifts of many membrane proteins occur (Zhang et al., 2018), and show that in some cases these shifts in the proteins are in the range of 0.5-1.5 nm (Bae et al., 2015; Islas, 2016; Bezanilla, 2018). Thus, shifts in the transmembrane potential are argued to alter the force imposed on the dipole molecules in the plasma membrane (Brownell et al., 2010). This shift in these membrane proteins would seem to be able to account for the widening reported to happen in the plasma membrane during an action potential (El Hady et al., 2015; Alcami et al., 2019). The change in light scattering which is reported to occur during APs is also noted to be associated with changes in the membrane potential (Perachia et al., 1971; Stepnoski et al., 1991). Thus, the electrophysiological AP model would suggest that a large transmembrane potential shift should have influences on the membrane dipole molecules of which proteins are the most dipolar and the most flexible.

These two models present very different views of the change in membrane width and changes in membrane optical features associated with APs. One way to test between these views would be to consider what each predicts. The electrophysiological AP model would suggest that the changes in width and optical features would be proportional to the extent of the transmembrane potential changes applied. Thus even changes in the membrane potential which would not induce an AP would be expected to produce influences on these associated features. The application of hyperpolarization treatments to the plasma membrane would thus not be expected to induce an AP firing, but would be expected to induce these sorts of shifts in protein conformational changes and so alter the optical features of the membrane. Such findings have been reported in several studies (Cohen et al., 1971; Tasaki, 1982; Oh et al., 2012; Lee et al., 2017). On the other hand, the soliton-AP model, while perhaps allowing that some small shifts of membrane dipole molecules in response to membrane potential shifts might occur, would seem to predict that these shifts in optical features and membrane width should be observed in association with a major lipid phase transition, and so under this model with a soliton-based AP. This view would seem to suggest that such a shift should thus be discrete, and should occur in a sudden fashion, as the lipid phase changes the soliton-AP model assumes to be happening are not partial events. Thus, the soliton-AP model might predict, if somehow a sudden lipid phase transition was induced that this would impose a sudden shift in membrane capacitance, membrane width, and membrane optical features in a distinct step-like manner, but only during actual AP firing. However, the lack of a pure phospholipid bilayer to show responses to a shift in transbilayer voltage was reported by Berestovsky et al. (1970, pg. 263) who, on examining this issue using a phospholipid bilayer under voltage clamp, noted; "On unmodified bimolecular membranes any optic effects under 100 mV voltage were not detected." That finding would seem to argue against a role for a transmembrane potential change to induce a lipid phase shift. More tests on these issues would, of course, be welcome, but there seems to be a clear path here for the advocates of the soliton-AP model to do tests which have a potential to give evidence in

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support of, or which might refute, their model, if they have the courage to make and report on such tests, as opposed to having the courage just to make assumptions.

What should we conclude

In terms then of the structural shifts seen in the plasma membrane during an AP, there seems to be much evidence which is consistent with the electrophysiological AP model's requirement that with changes in transmembrane potential changes in membrane molecular alignment and conformations occur. Thus, we may conclude that these features are likely voltage-dependent to a large extent. Concerning the soliton-AP model's prediction that these features are due to a major lipid phase transition, similar to a liquid-crystalline to gel transition, we are in a similar position to what was encountered in our consideration of capacitance shifts during APs in that the argument put forward by the advocates for the soliton-AP model would be much stronger IF they first presented actual evidence for such a lipid phase transition happening during an AP. Instead, their argument seems to be, once again, implying that these circumstantial features should be taken as evidence in the place of actual detection of their model's presumed lipid phase transition. This argument is not very compelling for two reasons. First, these features are rather well accounted for under the electrophysiological AP model, so strong evidence would seem to be needed to compel us to reject those findings. Second, as Heimburg (2007, pg. 311) himself noted, mere association should not be taken as "proof," and so it would seem reasonable to ask for clear and compelling evidence that a major lipid phase transition actually happens during an AP before considering what consequences it might have. To do otherwise would seem to be arguing ahead of the available evidence.

On the Electrical Features of the AP

Of course the AP displays a distinctive pattern of electrical potential changes (Hodgkin et al., 1945), with a rapid initial depolarization phase, followed by a longer and slower hyperpolarization phase, before returning to the normal transmembrane resting potential (Hille, 2001; Massey et al., 2022). Thus, while the advocates for the soliton-AP model point out, quite rightly, that more seems to be going on during an AP than just this pattern of electrical changes (Heimburg et al., 2005), this pattern of electrical potential changes is still a major feature of an AP. Therefore, any model which attempts to account for AP features should reasonably be expected to offer a means to account for this AP pattern of electrical changes, as well as accounting for any other features that it might also choose to address. Therefore, let us next consider first how the electrophysiological AP model accounts for the typical AP pattern of electrical changes, and then consider how the soliton-AP model attempts to account for this pattern as well.

Based on early evidence, it was concluded that AP transmission is done through the spread of electrical field changes (Hodgkin, 1937a, 1937b). The modern electrophysiological AP model makes use of the reported and well replicated finding that during an AP in neurons there is an initial transient rise in membrane permeability, typically to Na^+, followed later by a slower transient rise in K^+ permeability (Hodgkin et al., 1949a, 1952b, 1952c, 1952d, 1952e; Shepherd, 1988a; Hille, 2001). The discovery of voltage-gated protein-based ion channels and the study of their properties (Neher et al., 1976, 1982; Sigworth et al., 1980; Chiu et al., 1982; Auerbach et al., 1984; Jackson, 1984; Sakmann et al., 1984; Stern et al., 1990; Begenisich, 1992; Jones et al., 1994; Ayer et al., 1997; Cha et al., 1997; Thiel et al., 1997; Doyle et al., 1998; Sonnleitner et al., 2002; Cardnell et al., 2006; Valiyaveetil et al., 2006; Bean, 2007; Lorincz et al., 2010; Schroeter et al., 2010; Jensen et al., 2012; Kariev et al., 2012; Braun, 2013; de Lera Ruiz et al., 2015; Islas, 2016; Kim et al., 2016b; Kratochvil et al., 2016; Whicher et al., 2016; Catterall, 2017; Ma et al., 2017; Roux, 2017; Shen et al., 2017, 2018, 2019; McClintock et al., 2018; Pal et al., 2018; Pan et al., 2018, 2019; Touska et al., 2018; Wulf et al., 2018; Clairfeuille et al., 2019; Schewe et al., 2019; Sun et al., 2019; Chakrabarti et al., 2024) has been broadly accepted to account for this classically observed change in membrane permeability during an AP. This pattern of change in permeability, coupled with the electrochemical energy gradients for Na^+ and K^+ across the plasma membrane, thus lead during an AP to there being an initial inward Na^+ current, followed by a slightly

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longer and lower K^+ outward current. That such currents occur has been well documented (Hodgkin et al., 1952b; Hodgkin et al., 1955; Cole et al., 1960; Narahashi, 1965; Guttman et al., 1970; Hille, 2001; Carter et al., 2009; Fleidervish et al., 2010). This movement of ions across the membrane has electrical consequences, in a manner consistent with the law of conservation of charge, Ohm's law, and with the Maxwell equations (Jackson, 1999; Lucht, 2014). Thus, after assembling the initial measurements of the ionic currents which were reported, the resistances measured to be involved, and other related electrical features of the neuron, Hodgkin and Huxley (1952a) were able to confirm that this set of information, with some additional assumptions, was adequate to allow for the deriving of an initial set of empirical equations which could model many of the electrical features of the AP. Concering these equations, a common mistake often made by some (Carrillo, 2025) is to refer to these equations as "the" Hodgkin-Huxley AP model. But it should be noted that Hodgkin and Huxley (1952a) themselves state that merely deriving such an empirical equation set was not proof that it was the only way to describe an AP, and they emphasized that the equations they presented were mainly used to test the adequacy of the state of knowledge at that time and so test their model. Thus the Hodgkin and Huxley model is not the equations, but rather the descriptive narrative of cause and effect links they discovered, and so the specific equations are not of critical importance. Indeed, many other versions of equations have been derived to account for various features of APs, for instance see Sangrey et al. (2004). Therefore, what is important is not the equations per say, but that the electrophysiological AP model has evidence for the transmembrane ion movements and other features which it takes as the basis for production of the pattern of electrical potential shifts seen during an AP and also can be related to each ion's transmembrane electrochemcial energy gradient which drive the ion flows in a manner consistent with the law of conservation of energy. Later it was found that these ion flows can be related to the properties of the voltage-gated protein-based ion channels in the membrane. This is a brief outline of how the electrophysiological AP model accounts for the electrical features of an AP.

Next, let us consider how the soliton-AP model (Heimburg et al., 2005) would account for the pattern of shifts in electrical potential seen across an AP. Under this model it is proposed that the hypothesized lipid phase transition has as one of its effects an alteration of the density of the lipids per area on each face of the membrane. This is suggested to alter the surface charge density, and with the two faces of the membranes being different in composition then a difference in the surface charge density change on one face versus the other may result during a lipid phase transition which is assumed to happen in both membrane faces during an AP. Thus, surface potential changes are proposed to occur during the presumed lipid phase transition which the soliton-AP model assumes happens, and this difference in surface potential shifts on the two membrane faces is how this model proposes to account for the electrical pattern we see during an AP (Heimburg et al., 2006; Fichtl et al., 2016; Mussel et al., 2019, 2021; Meissner, 2022). Here it has been suggested (Heimburg et al., 2006, pg. 8) that: "... it seems plausible that mechanical solitons can generate voltage changes comparable to those observed during the action potential. The exact values remain to be determined by experiment." Oddly, this experimental determination, to which Heimburg et al. (2006) refers, seems to have not yet been reported by the advocates of the soliton-AP model? There are obvious experiments which might be done to test this claim, as noted in Meissner (2022), but results of any such tests have not yet been reported. Therefore, a major assumption being made here is that surface potential changes, which might well happen during any presumed lipid phase transition event (if one actually occurs), would have macroscopic effects and be observable as transmembrane potential changes. It is thus largely through this untested and unconfirmed assumption, of surface potentials being macroscopic in their influence, that the soliton-AP model attempts to account for the pattern of electrical features seen during a typical AP. Let us examine this issue further.

That APs are macroscopic in their electrical influence is well supported by the reported data. For instance, Heimburg's own lab group positioned electrodes at some distance away from an isolated nerve bundle and were able to detect the passage of compound APs in it, even though the electrodes were many micrometers to millimeters away from the cells producing the compound APs (Gonzalez-

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Perez et al., 2014). EEG recordings of the AP activity activities in brain tissue are commonly done even though these electrodes are many cell diameters away from the actual cells producing the APs (Cavanagh, 2018). Thus the ability for APs to be monitored by microelectrodes at a considerable distance away from an excitable membrane indicates that APs have a macroscopic influence. One question then, is whether surface potential changes can also be detected by positioning microelectrodes at such distances away from the cell membrane.

Thus, while it has been reported that with a phase transition in a phospholipid bilayer there can be changes in surface potentials (Träuble et al., 1974), two problems with the soliton-AP model's attempt to use surface potentials to account for the electrical features seen in an AP, as described previously (Meissner, 2022), are that surface potentials are well known to just be microscopic in nature only extending out about a nanometer, and also that surface potentials are noted to be distinct from the transmembrane potential seen across biological membranes (Beitinger et al., 1989; Wang, 2012; Galassi et al., 2021; Zhou et al., 2022). The short distance of influence of surface potentials is noted to be related to the dipole nature of water and ions which by shielding surface potentials often limit surface potential effects to about one nanometer or less under physiological conditions (Klausen et al., 2016; Meissner, 2022). Thus, for a surface potential to have its influence extend over a considerable distance the surrounding medium must not contain dipole molecules, such as water or ions, rather only when examined in air or vacuum are the influences of surface potentials often seen to be able to spread out to micrometer to millimeter distances. So with the influence of surface potentials only extending a nanometer or so outward in physiological conditions, microelectrodes are typically unable to detect surface potentials, and other methods are used to detect surface potentials (Mesquida et al., 2018; Meissner, 2022). Thus APs are macroscopic and taken to reflect transmembrane potential changes, while surface potential shifts are microscopic and seem to be unable to account for the macroscopic electrical features of the AP.

None of the above is meant to dismiss the importance of surface potentials or their influence on membrane properties. For instance, recall that in the above consideration of membrane capacitance changes during APs it was noted how surface potential changes can be one means to account for changes seen in membrane capacitance. Also, changes in surface potentials are reported to be able to influence the activities of membrane or local peripheral proteins (Beitinger et al., 1989; Goldenberg et al., 2010; Wang, 2012; Zhou et al., 2022; Westendorff et al., 2024) and so may have a variety of effects. The intent here is to point out that for the soliton-AP model to depend on surface potential shifts to account for the pattern of electrical changes seen during an AP there is an assumption being made that surface potentials, under physiological conditions, have macroscopic influences. No evidence in support this assumption seems to have yet been presented, and so this challenges the soliton-AP model's ability to account for known AP electrical features.

What should we conclude

So in attempting to account for just the pattern of electrical potential changes seen during a typical AP, these two models offer very different views. The electrophysiological AP model is well supported by reproducible findings, and operates in a manner consistent with known physical laws and principles. In contrast, the soliton-AP model, again, builds on its as of yet unconfirmed assumption that the AP is based on a lipid phase transition, and adds in addition the assumption that surface potential changes would contribute to transmembrane potential shifts, and so act in a macroscopic manner and thus be able to account for the electrical features of an AP. Thus, to have these claims for the soliton-AP model accepted much more evidence about surface potentials and their influences would need to be presented by the advocates of this model. Several obvious tests along these lines were presented earlier (Meissner, 2022), but, so far, no positive results of such tests have been reported. Without such positive findings, the proposal that surface potential changes have macroscopic influences seems to be without factual support and so is a mere unconfirmed hypothesis. In contrast, the electrophysiological AP model, as noted above, has much supportive evidence on its side. Thus, we are faced, again, with a well supported model with strong evidence behind it on the one hand, and a set of conjectures not yet demonstrated to be valid on the other. Until that situation

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changes, the electrophysiological AP model's accounting of the electrical features of the AP should continue to be accepted.

About the Hypothesis of AP Wave Length

As mentioned previously, one of the differences between the electrophysiological AP model and the soliton-AP model is how they arrange events in terms of cause-and-effect in each case. The electrophysiological AP model has the electrical potential changes which occur as the cause of various physical changes seen during an AP (Cohen, 1973; El Hady et al., 2015). In contrast, the soliton-AP model assumes that the AP is a physical wave, based on a presumed traveling lipid phase transition, and claims that one of the side effects of this physical wave is the electrical features of an action potential (Heimburg et al., 2006; Heimburg, 2025). Thus, these two models differ in how they arrange AP events in terms of cause-and-effect. Here we will consider yet another area where this inversion of cause-and-effect seems to occur, and note how the assumption that the AP is a physical wave applies to just one of these two models and not to the other.

In his recent article, Heimburg (2025) suggests that if the AP is indeed a physical wave, then the full pattern of electrical potential changes seen across the AP would be assumed to represent one cycle of that physical wave. What this implies is that at one point along an axon the membrane potential may be at one point in the cycle of the AP electrical pattern, while at another point further down the axon, the membrane potential would be different as the AP "wave" would be at a different point along its wavelength. Heimburg (2025, see his Eq. 1) then suggests that given a typical duration of an AP, and a typical AP velocity, this implies that this hypothetical physical wave would be in many cases rather long. Depending on AP duration and velocity, estimates of a presumed wavelength for the AP from 4 mm to 51 cm are suggested by Heimburg (2025), and he goes on to note that this would be much longer than the length of many of the neurons in which the AP occurs! This, he then claims, implies that under his soliton-AP model an AP may be a multicellular phenomenon, as it would not, apparently, fit within a single cell. One odd thing here is, if the AP is truly to be considered to be a wave as long or longer then the neuron in which it occurs, then why does Heimburg often present an illustration of a soliton-AP as happening only in a small fraction of the length of an axon (for instance, see Heimburg, 2025, his Fig. 15)? Another oddity, is that there are clear reports of APs examined in cells grown in cell culture, and so are isolated from other cells (Stepnoski et al., 1991; Batabyal et al., 2017), which implies that in many cases the AP does fit within a single cell. This would seem to challenge Heimburg's (2025) suggestion that APs are often larger than the cell which generates them?

It should be noted that the electrophysiological AP model does not view an AP as a physical wave, rather this model views an AP as an electrical field shift which happens to have some physical effects which are considered to be secondary in nature (El Hady et al., 2015; Yang et al., 2018; Ling et al., 2020). According to the electrophysiological AP model in a myelinated axon all the events relating to ion current flow needed for the generation of the full pattern of electrical changes during an AP occur at one node, and are not displaced over space, in contrast to what is suggested by Heimburg (2025). Thus, unlike the above soliton-AP model, there is no physical wave happening under the electrophysiological AP model. Rather, under the electrophysiological AP model an electrical field shift at a node in a myelinated axon would need to have enough influence to alter the electrical potential at the next node to induce the firing of a new AP at that next node. The extent of the influence of this electrical field over distance depends on the nature of the medium present, in this case the cytosol and the extracellular solution in the tissue. Water, ions, and any dipole molecules in these solutions can significantly alter the influence of a local electrical shift across distance. Electrophysiologists account for this via the resistance of the medium and of the membrane, and by its capacitance, all of which influence how far and how rapidly an electrical field shift can extend its influence. These aspects of the electrophysiological AP have been studied and are well documented (Taskai, 1939; Huxley et al., 1949; Frankenhaeuser et al., 1964; Gentet et al., 2000). If, for whatever reason, the electrical field shift is too weak to sufficiently influence the voltage-sensitive protein-

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based ion channels at the next node, then no new AP will be fired at that next node. Or if the voltage-sensing protein-based ion channels at the next node are inhibited in some manner so that they can not respond, then the electrical field of the AP from one node would have to extend to another node further down the axon and its influence there will be lower and slower due to the added distance. This is not at all like a physical wave which would just keep traveling, showing little or no diminishment with distance. Instead, this might be viewed as analogous to light from a light bulb which decreases in intensity with distance, and so becomes less able to induce, say, a light sensor which requires a certain threshold of light intensity to activate a system to turn on a new light bulb at a new location. Notice then, that in this view, and AP is not a physical wave, and does not have an inherent wavelength. All the events needed for the full pattern of electrical changes seen during an AP occur at one location without movement of any physical wave down the axon.

Thus the soliton-AP model by viewing the AP as a physical wave, and by suggesting that it does not dissipate with distance (Heimburg, 2025) is taking a very different view compared to the electrophysiological AP model which views the AP as an electrical field which does attenuate with distance.

With regard then to his proposal that an AP is a physical wave of large size, Heimburg (2025; pg. 3) suggests that this makes it possible to view the AP as a "macroscopic" event, "... and that for this reason a macroscopic thermodynamic treatment of the nerve membrane properties is justified." The good Prof. Heimburg does not state explicitly just what macroscopic thermodynamic style of analysis he would suggest to be possible for a macroscopic process versus not possible for a microscopic one, or why a phenomenon needs to be macroscopic in size to "justify" the use of thermodynamics? This leaves a reader with the impression that perhaps he is implying that thermodynamics does not apply to microscopic events? If so, that would be a rather odd suggestion, since there are thermodynamic studies with regard to a variety of processes done at the molecular level (Flodgaard et al., 1974; Gluick et al., 1994; Brauchi et al., 2004; Khvorostyanov et al., 2004; Sehgal et al., 2006; Curnow et al., 2007; Isom et al., 2011; Huang et al., 2014; Zhao, 2015; Smith et al., 2016), not to mention studies of the thermodynamics of lipid bilayer phase transitions (Heimburg, 1998; Matsuki et al., 2019), which are surely thermodynamic studies of microscopic events at the molecular level. With regard to one thermodynamic study of the AP, done in a manner which does not seem to require any assumption as to the physical size of the AP, there is the work done by Hodgkin et al. (1949b). Hodgkin et al. (1949b) were able to determine the temperature sensitivity of the initial rapid depolarization part of the AP versus that of the later slower hyperpolarization stage of the AP. They report that these two parts of an AP display very different temperature sensitivities, and so have different Q_{10} values. The electrophysicological AP model notes that these two parts of the AP are each dominated by distinct voltage-gated protein-based ion channels, first a Na^+ channel and then a K^+ channel (Hille, 2001), and this suggests that one reason for the difference in the Q_{10} values in these two AP stages may be due to the involvement of different proteins each with a different temperature sensitivity. Thus Hodgkin et al. (1949b) is a thermodynamic study, of a microscopic system, which tells us something about events during AP firing. Just how the soliton-AP model would account for the finding made by Hodgkin et al. (1949b), that there are different Q_{10} values at different stages of an AP, is a thermodynamic question which the advocates of the soliton-AP model seem to not have addressed. But this article by Hodgkin et al. (1949b) is perhaps a good illustration of a thermodynamic study of aspects of the AP which seems to be valid without having to assume that the AP is a physically large wave. Thus why Heimburg (2025) seems to imply a need for APs to be physically macroscopic to justify their study via thermodynamic methods is a bit unclear.

What should we conclude

Recall that the soliton-AP model assumes that a lipid phase transition occurs in association with an AP. Heimburg (2025) is next noting an implication of this phase transition acting as a physical wave in that like all waves it would have a wavelength. Thus we are, once again, seeing assumption placed on top of assumption without first being presented with any clear evidence that the initial assumption is valid. In any event, any features or limitations that this AP-as-a-physical-wave

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assumption imposes would seem to apply to the soliton-AP model alone, and have no apparent relevance to the electrophysiological AP model which considers the AP not to be a physical wave. Contrast this with the evidence noted above for how the electrophysiological AP model would account for how one AP fired at one location has, through its electrical field shifts, the ability to influence the firing of a new AP further down an axon. Thus, we have, again, a hypothesis without clear evidence, versus another which has evidence reported which supports it. Therefore, once again, these speculations from the soliton-AP model, while interesting on some levels, should not be accepted until there is clear evidence presented for them. The most important evidence in this case, which is still lacking, being actual evidence that a major lipid phase transition happens during an AP.

Concerning the Mechanical Synapse Hypothesis

Along with his claim that an AP is a large physical wave, Heimburg (2025) now also claims that a lipid liquid-crystalline to gel phase change during an AP would contract the length of the plasma membrane significantly. Based on his calculations Heimburg (2025; pg. 10) states; "We obtain a change in length of the total axon of 2.58 cm..." in one case, and for another suggests there should be "... a contraction of the axon by 1.44 cm..." In an attempt to support this claim, Heimburg (2025) notes work (Tasaki et al., 1980, 1982, 1989) which reports that longitudinal contractions of from 5 nm up to 80 nm have been observed during AP firings in isolated nerve tissues. Obviously a contraction of 80 nm is quite different from that of 1-2 cm which is what Heimburg (2025) suggests should occur, and on this point Heimburg (2025, pg. 11) states; "This is much less than what the soliton theory predicts but it is qualitatively in the same direction." In this way Heimburg (2025) attempts to account for a six order of magnitude difference between what is predicted and what is observed! It might be reasonable to suggest that such a difference between prediction and observation alone might be enough to bring the prediction into question? Heimburg's suggestion that a contraction of hundreds of micrometers to centimeters should occur with every AP firing in many neurons would seem to be easily checked by a rather basic direct and simple observation. Yet Heimburg (2025) himself offers no direct evidence of such an event of the magnitude he suggests, but rather makes the assumption that this would occur based on the soliton-AP model's previous assumption that a major lipid phase transition happens during APs.

Another problem with Heimburg's (2025) argument, that there is significant contraction of a cell during AP firings, is that Tasaki et al. (1982, 1989) showed that the contractions observed occur on a longer time scale than that of the immediate AP, and that summation can occur across several AP firings. Indeed, Tasaki et al. (1989, pg. 1036) notes this where they state; "The duration of the mechanical responses recorded in this manner was considerably longer than the mechanical changes recorded in the transverse direction." The transverse swelling being associated with individual AP firings and not showing this longitudinally-related summation. And in earlier work Tasaki et al. (1982, pg. 1438) notes; "This period is far longer than the time required for propagation of an impulse along the 20 mm long portion of the nerve (approximately 5 msec)." Therefore, Tasaki et al. (1990) notes that the summed changes in length from several AP firings can add up and occur over a much longer time scale than does any single AP firing. Thus, if the electrical features of the AP, as suggested under the soliton-AP model, are to be coupled to a presumed change in lipid phase states and so coupled to its likely radial change in width (Heimburg et al., 2006), and if longitudinal contractions of the axon are now also to be coupled to this same assumed lipid phase transition (Heimburg, 2025), then they should all be expected to share the same temporal pattern. Since they do not, that implies different mechanisms are perhaps operating? One mechanism which is suggested by Tasaki et al. (1990) is that ion entry into the axon may have effects on the cytoskeleton, or effects on the colloidal-like cytosol (Tasaki et al., 1982), and notes that these may help account for the volume change found to occur in an axon with multiple AP firings (Tasaki et al., 1990). It should be noted that Heimburg's (2025) calculations of what his soliton-AP model might predict in terms of axon contraction with AP firing assumed a constant cell volume; an assumption which seems to be contradicted by observation (Cohen, 1973; Tasaki et al., 1982, 1990). Thus, Heimburg's (2025) calculations seem to be at odds with

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observed magnitudes of contraction, with the observed temporal patterns, and are based on assumptions which have not, yet, been found to be supported by actual data from actual measurements.

Having put forward an argument for the AP to be a physical wave which extends across many centimeters, and for its being accompanied by a significant physical shortening in axon length, Heimburg (2025, pg. 6) then suggests an implication of this with regard to synapses: "In a hydrodynamic picture of the nerve pulse, the pulse might not see a synapse at all and will cross the distance of the synaptic gap with the speed of the soliton because the synapse itself is part of a macroscopic motion." Thus, Heimburg (2025) proposes a new "mechanical synapse" concept for consideration. The previous concepts of synaptic connections include both electrical and chemical synapses (Shepherd, 1988b; Hormuzdi et al., 2004; Koester et al., 2005; Sanes et al., 2006; Perea et al., 2007; Bissiere et al., 2011; Haas et al., 2011; Hestrin, 2011; Sylwestrak et al., 2012; O'Brien, 2014; Favuzzi et al., 2019; Groc et al., 2020; Cárdenas-García et al., 2024; Vandael et al., 2024) and it may be noted that there can be variation in speeds of transmission across different chemical synaptic types as well (Greengard, 2001). Whether Heimburg (2025) is proposing a mechanical synapse in addition to these already well established synaptic types, or if he is suggesting to sweep them aside in favor of his new concept of mechanical synapses is unclear from his article. Heimburg (2025, pg. 12) claims support for his concept of a mechanical synapse by stating: "Mechanical motion of the synapse in the nanometer range has in fact directly been measured in mammalian nerve terminals (Kim et al., 2007)." We will next, therefore, consider this work by Kim et al. (2007), and find that this claim by Heimburg seems not to be upheld.

The suggestion by Heimburg (2025) that Kim et al. (2007) examined events at the synapses between neurons seems to be a mischaracterization of the work by Kim et al. (2007). That work examined the neurohypophysis tissue, which is noted to be a neurosecretory structure for the release of hormones into the blood stream, and so AP induced secretion was the focus of that work and not AP transmission across synapses, as secretion into the bloodstream is distinct from cell-to-cell synaptic connections. Furthermore, nowhere in Kim et al. (2007) is there any mention made of mechanical distentions in the longitudinal orientation, rather the increase is in radial thickness (i.e., vertically or transversely). This rise in thickness is described by Kim et al. (2007) to be dependent on the presence of extracellular Na^+ and so is suggested to be an osmotic effect, as is supported by the following reported observation (Kim et al., 2007, pg. 3124): "The disproportionate decrease in amplitude of the mechanical spike and the broadening of the signal in the reduced-Na^+ Ringer's solution are evident." It is true, as Heimburg (2025) claims, that Kim et al. (2007) noted that a swelling of about 5 nm was observed across this tissue upon AP arrival to it, but this was a vertical swelling, not a longitudinal one, and also in this work there was summation across many cells and so this should not be taken as an observation at the single cell level. This is indicated where Kim et al. (2007, pg. 3126) notes that they were working at the tissue level and states: "Since the tissue probably owes its thickness to a stack of ~100 terminals, this deflection may reflect an increase in diameter of as little as 0.05 nm (0.5 Å) in a single terminal." Thus the vertical displacement (i.e., "an increase in diameter") is suggested by Kim et al. (2007, pg. 3126) to be very small when considered at the cellular level, and that it may be accounted for by osmotic effects which are expected to arise with AP arrival and secretory actions in this tissue. Thus, Heimburg's (2025) claims concerning the meaning of the evidence presented by Kim et al. (2007) appears to be unsupported by what is actually presented there, as Kim et al. (2007) do not report any observation of longitudinal contractions happening at cell-to-cell synaptic areas.

What should we conclude

Given that under the electrophysiological AP model the AP is not considered to be a physical wave, all of Heimburg's (2025) comments about how a physical wave-based AP may or may not fit into a single cell, or about the contraction in length that it might induce, would seem to be issues which only the soliton-AP model should be expected to address. But our good Prof. Heimburg has not offered compelling evidence based on actual observations that such a major contraction actually

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occurs in reality. Nor has he offered support for his implication that some sort of "mechanical synapse" operates to allow the transmission of an AP from an axon terminus into a dendritic arm of the next neuron. Rather, starting with his assumption of a major lipid phase change as the basis for an AP, an implication of a longitudinal contraction is said to be expected. The fact that no contraction of the magnitude he suggests has in fact been reported, would seem to be a major reason for rejecting this suggestion, as it seems odd to propose that neurobiologists who have long observed neurons *in vivo*, *in situ*, and in cell culture would have to be assumed to have somehow not noticed AP-associated neuron contractions in the 0.1-10 mm range? This proposed magnitude of contraction should be visible to the naked eye, or easily seen under a common dissecting microscopy. Which implies that our good Prof. Heimburg should have little difficulty obtaining actual direct observational evidence in this case? Heimburg's (2025) mischaracterization of the work reported in Kim et al. (2007), who reported vertical shifts rather than longitudinal ones, simply adds additional doubt to the argument he presents.

This all seems to suggest that such incredible belief is placed in the soliton-AP model that any implication derived from it is given high levels of confidence, without any testing of such items being done or even being suggested to need to be done. Thus, we are brought to a consideration of standards of evidence: Heimburg offers no actual evidence of lipid phase shifts, only a theoretical conjecture, but one in which he has such high confidence that he apparently thinks that alone should compel its acceptance. In science we should be willing to go where rigorous evidence forces us to go, but we must insist on having actual reproducible evidence presented. In this case, where no compelling evidence is presented, there can be no acceptance of the stated claims, at this time.

On Energy Issues and the AP Passage Hypothesis

Another aspect of the soliton-AP model which deserves some attention is the energy shift needed to initiate the sort of lipid phase change that this model assumes is happening during an AP. Both Heimburg et al. (2006) and Mosgaard et al. (2015) present estimates of the energy change per mole of lipid which would be expected with a liquid-crystalline to gel phase transition. They base their calculations on a DPPC lipid bilayer's phase transition, and note the temperature of melting (T_m) at which the free energy change for this lipid phase change would be zero, and so phase transitions would be likely to happen at that temperature. Obviously the further the actual temperature is from this T_m value then a larger level of energy change would be needed to induce a lipid phase transition (Heimburg, 2023). In this way an estimate of the energy shift needed for a lipid phase transition to be possible at a temperature other than the T_m of the system can be made. Of course the energy for this might come from any of a number of sources, and Heimburg (2022a) does describe several possibilities, none of which are as of yet confirmed. However, it should be noted that a plasma membrane is not a DPPC bilayer, and a plasma membrane's T_m, if it has one, as well as enthalpy and entropy of any phase transition, may be different from what Heimburg et al. (2006) and Mosgaard et al. (2015) assume by using values from a DPPC bilayer. But at least the use of a DPPC bilayer as a base model can give an initial estimate of the energy change for such a system in terms of joules per mole of phase transitioning lipid. Where the energy to induce this presumed lipid phase shift in a plasma membrane would come from is an issue that the soliton-AP model does not explicitly address, and so how the energy is to be supplied to achieved this presumed phase transition is still unclear.

Be that as it may, obviously if the plasma membrane of a neuron has a T_m which might be taken to be ten or more degrees C away from the normal body temperature, which is what the advocates for the soliton-AP model suggest (Mužić et al., 2019), then the greater the difference in ambient temperature from this T_m the higher of an energy shift would need to be arranged to induce a soliton-based AP firing under the soliton-AP model. Also, if more lipid molecules are to engage in this transition, then the energy demand goes up; note that the estimates made by Heimburg et al. (2006) and Mosgaard et al (2015) are for energy per mole of lipid transition, so more lipid molecules transitioning implies a higher total energy cost. Thus, when Heimburg (2025) suggests that the proposed lipid transition thought to occur during an AP may cover many centimeters of cell length,

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that would seem to imply that the total energy shift needed to induce a phase transition across that much of the cell all at once would need to be much larger? Where does that energy come from?

Consider also how cell morphology may influence this energy demand. Axons are known to branch many times (Catalano et al., 1995; Wittner et al., 2007; Brown et al., 2008; Economo et al., 2016; Liu et al., 2024), and so if we assume one soliton-wave based on a lipid phase transition is happening in a neuron's axon, by moving down that axon it may well end up going into perhaps a hundred branches of that axon to many termini. Thus one soliton based on a traveling lipid phase transition would need to result in over a hundred such waves of transition all being produced in this same cell. This expands the number of lipid molecules involved greatly, so where does the energy shift needed for this come from? Pissadaki et al. (2013) did an analysis which suggests that there would be expected to be a rise in energy cost per AP transmission with more branching of a cell. We are also told that under the soliton-AP model this presumed lipid phase transition wave should be adiabatic and self perpetuating, with no net heat (Heimburg, 2025). So if such a soliton comes to a branch in an axon, as it should, does the energy of the original soliton wave somehow get divided in half so that each branch now has a soliton with a lower energy content per mole of lipid transitioned? Or does the soliton-AP model suggest that somehow there is an energy adjustment made at each axon branch point so that the original energy of the soliton per mole of phase transitioned lipid is maintained? If so, how would that be done in an adiabatic manner? Thus, there are questions of energy relations here which the soliton-AP model seems not to have addressed explicitly.

Going further, consider a case where we have a single neuron grown in cell culture which displays APs, but which is an isolated cell and so has no synapses onto other cells and none onto itself from other cells. Also consider the concept of a soliton wave-based AP which should pass through other APs upon collision (Heimburg, 2025). We might envision an AP moving down the axon, as Heimburg (2025, see his Fig. 15) presents it, as a cylinder of lipid phase transition moving as a physical wave. When it gets to an axon terminus this soliton comes in from all sides of this cylindrical wave and effectively collides with itself at the cell terminus. According to Heimburg (2025), and others (Gonzalez-Perez et al., 2014), such a colliding soliton would be expected to pass through itself, and proceed to then travel back up the axon away from the axon terminus? Now, consider this happening in a neuron with an axon which branches and leads to a hundred axon termini. Each terminus would have this soliton wave reach its tip, pass through itself, as Heimburg (2025) clearly suggests that AP passage upon collision is part of his soliton-AP model, and then start traveling back up the axon. Thus where one soliton/lipid phase transition wave would have started down the main axon, a hundred such waves then come back up the axon, and since the branches are likely to be of different lengths these back flowing waves would likely not be in sync with one another. On getting to the dendritic termini of this cell, a similar set of rebounding would perhaps happen, and so on. Where would the energy needed to power all of this amplification of soliton waves come from? Note, that this example assumes an isolated cell, without synapses, in cell culture, so the energy is not jumping into other cells, nor coming in from other cells either, as Heimburg (2025) might argue under his new "mechanical synapse" concept.

Of course, the advocates for the soliton AP model have also not yet clearly identified how the energy shift needed to initiate their soliton AP is coupled in a cell to achieve the start of their presumed lipid phase transition wave in the cell. Heimburg (2012, pg. 921) notes that a typical phospholipid bilayer would have its T_m shifted just by 0.0114°K by an applied trans-bilayer potential shift of 100 mV, which seems to exclude a voltage change-based induction of any presumed lipid phase transition? Thus, once again, if we had evidence of an actual lipid phase shift happening during an AP, then studies of how it is initiated might be possible. But, clearly, looking for a mechanism to start something no one has yet detected to be happening is a tough assignment. Similarly, how a soliton AP would be terminated has not been described by the advocates of the soliton AP model either. Which is understandable as to study how something is ended, there first needs to be given solid evidence of its occurrence. But if, as Heimburg (2025) argues, soliton APs should not annihilate upon collision, and do not dissipate, then how are they ended? And if, as Heimburg (2025) suggests,

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soliton passage occurs, then should we not expect one AP to rebound in an isolated cell and come back from the axon termini as many separate APs?

It should be noted that the electrophysiological AP model has largely addressed these issues: How an AP is initiated, the role of the refractory period in AP annihilation upon collision, and what happens at axon termini to terminate APs there have been described. Also by tapping into the transmembrane electrochemical potential gradients for sodium and potassium ions this largely accounts for the powering of the electrophysiological AP. These issues are well described in many standard texts (Aizawa et al., 1975; Tasaki, 1982; Shepherd, 1988a; Hille, 2001; Luo, 2016; Massey et al., 2022). The consensus is that the AP process produces net heat, so an energy change is indicated, a view which is characterized by Abbott et al. (1958. pg. 176); "It is difficult indeed to imagine an excitable membrane going through a complete cycle involving a several 100-fold increase in permeability to Na ions, followed by a similar increase in permeability to K ions, and yet behaving as a conservation system without change of energy..."

In contrast, the proposal made by Heimburg's group is that a soliton-AP has no net energy change, and that upon AP collision there is passage of the APs through each other. However, the published report of AP passage through each other upon collision was based on the use of a nerve bundle (Gonzalez-Perez et al., 2014; Gonzalez-Perez et al., 2016; Wang et al., 2017), which led to questions as to whether the APs which were reported to have passed by each other were even in the same cell (Meissner, 2018). Work which explicitly tested what happens upon AP collision has found that, upon collision of two APs in the same cell, AP annihilation occurred and not AP passage (Fillafer et al., 2017). And it should be recalled that use is made of AP collisions leading to annihilation in the mapping of neuron connections between regions of the brain (Yeomans, 1995; Jones et al., 1999; Kelly et al., 2001). Thus annihilation upon AP collision is a commonly accepted feature (Berg et al., 2017).

What should we conclude

Without clear answers to these energy issues, one gets an impression of solitons operating as a sort of perpetual motion device - never dissipating, never ending, producing ever increasing numbers of such waves in a cell and ending up with more energy change being indicated than was put in to start the initial solitonic phase change. There is a question here as to whether this soliton-AP model may violate the law of conservation of energy? To address this, there needs first to be solid evidence given that a lipid phase transition happens during an AP. Once that is obtained, then studies of how it may be initiated, or terminated, and the energies involved might become possible. But until reproducible evidence of this assumed lipid phase change is actually presented, further progress on this question of energy relations seems likely to be difficult to achieve. Until such positive evidence is presented, the electrophysiological AP model would seem to remain therefore as the better model in terms of its accounting for the energetics of the AP.

Does an AP Generate Net Heat or Not?

In arguing for his soliton-AP model Heimburg (2025) cites his earlier work in which he claims (Heimburg, 2021, pg. 26): "It has long been known that there is no measurable heat production associated with the nerve pulse." We will see that there are no modern measurements that support this claim, rather Heimburg's (2025) claim that an AP generates no net heat is, it seems, merely a statement of what would be expected if his soliton-AP model is assumed to be correct. Therefore, let us look more closely at the evidence which relates to this claim of the AP having no net heat generated.

In his article Heimburg (2021, pg. 36) also states; "Within experimental accuracy, no heat is dissipated during the action potential (Abbott et al., 1958)." But the Abbott et al. (1958) article clearly presents their conclusion that there IS net heat from each AP firing (Table 1A). Thus Heimburg (2021) is citing Abbott et al. (1958) in support of something which is contradicted by the very item Heimburg cites. What Abbott et al. (1958) found, and later confirmed (Abbott et al., 1965), was that there is an initial positive heat emitted during the initial part of the AP, followed by a period of negative heat

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(an absorption of heat) during the later part of the AP, and that these two levels of heat are not equal in absolute magnitude, and so, with the positive heat somewhat higher than the negative heat (Table 1B), this results in an overall net heat from each AP. Other articles, which were cited by Heimburg (2025), also present conclusions that seem at odds with Heimburg's claim that APs lack net heat (Table 1). Thus, Heimburg is claiming that the positive heat, and the negative heat, would be equal in absolute magnitude, and so the AP process would be adiabatic. But this claim seems contradicted by the very articles he cites (Table 1). We will next consider the findings of Abbott et al. (1965), to see if they are consistent with Heimburg's hypothesis that the AP is adiabatic and generates no net heat.

Table 1. Statements from articles, which were cited by Heimburg (2025), on the issue of the pattern of heat production reported in studies of action potentials and production of net heat.

Statement:	Source:
A.) "The positive heat averaged 8.8 X 10^{-6} cal/g, the negative heat 6.8 X 10^{-6} cal/g, and the net heat 2.0 X 10^{-6} cal/g. The negative heat was about 77% of the positive heat."	Abbott et al. 1958, pg. 157
B.) "There were two phases of heat production; 3.8 μcal/g of heat was evolved during the first 50 msec and then nearly 80% was reabsorbed, equivalent to a negative heat production of about 3 μcal/g."	Abbott et al. 1965, pg. 371
C.) "... it is abundantly clear from our experiments and those of previous investigators that the nerve temperature does not return to its initial level after the passage of an impulse."	Howarth et al. 1968, pg. 790
D.) "The timing of the heat changes is compatible with the inward and outward currents and in the nerve there is never an overall cooling - the net heat is always positive."	Abbott et al. 1973, pg. 126
E.) "The difference between the two phases is the residual heat at the end of the action potential is now referred to as the 'net heat.'"	Howarth 1975, pg. 425
F.) "Since the recovery process is not 100% efficient, an appreciable amount of chemical energy is degraded into heat, which can be measured with a sensitive thermopile or thermistor. Quite distinct from the metabolic or recovery heat... small changes in temperature occur that are direct thermodynamic consequences of the changes in the potential gradient across the membrane that necessarily accompany the nerve impulse."	Ritchie et al. 1985, pg. 454
G.) "The two phases of initial heat production, positive and negative, are nearly equal, but not exactly so."	Ritchie et al. 1985, pg. 459
H.) "The amount of heat absorbed during the negative phase varies widely between 45 and 85% of the heat evolved during the positive phase."	Tasaki et al. 1989, pg. 1033

The Abbott et al. (1965) article integrated the measurements they made to obtain an estimate of the mean positive and negative heats (n = 4 in each case) seen during the firing of a compound action potential in a nerve fiber. A statistical analysis of the presented findings suggests that there is a statistically significant difference between the absolute values of positive heat and negative heat reported (Table 2). This finding is consistent with the conclusion reached by Abbott et al. (1958) that there is net heat from AP firings, and contradicts directly Prof. Heimburg's (2021, 2025) claim that an AP is adiabatic and generates no net heat. Of course, one might argue that the results reported by Abbott et al. (1965) might be due to chance, but with an alpha level of 0.005 that chance would seem to be small (Table 2). But to refute such an argument we might look to other measurements, made by another study, to see if they support what Abbott et al. (1965) conclude, that AP firing does generate net heat.

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Table 2. Are the positive and negative heats generated during action potentials equal in absolute magnitude or not? Data from Abbott et al. (1965, pgs. 372-373) are considered. A Student's T test (Mendenhall, 1975) was used to test the difference of the absolute mean values relative to an expected difference of zero. The results support the conclusion that the difference of the absolute values of the mean positive heat and the mean negative heat do differ significantly from a value of zero (at an alpha level of 0.005), implying that action potentials do generate net heat.

	T test details:
Sample size for each individual mean (n):	4
Mean positive heat observed (μcal/g/impulse) (±standard deviation):	7.2 (±0.5)
Mean negative heat observed (μcal/g/impulse) (±standard deviation):	-4.8 (±1.1)
T-test statistic of difference of the means:	3.973
Degrees of Freedom:	6
Tabular T value at $\alpha = 0.005$:	3.707

The Abbott et al. (1965) mean values of heat were averaged over many different preparations, and that allowed the influence of extraneous variation to remain, resulting in a high variation in the measurements. A paired design, in which each preparation's positive and negative heats are directly compared, by taking a ratio of the absolute value of negative heat to positive heat, would remove some of these extraneous influences on the data. In this case Prof. Heimburg's hypothesis that an AP is adiabatic would imply that the ratio of the absolute value of the negative heat absorbed to the positive heat emitted should be one, while if there is net positive heat then this ratio should be significantly lower than one. Such a paired approach was taken by Howarth et al. (1968) in their study of the heat of compound action potentials. Statistical analyses of two sets of data from their article are presented in Table 3, and in both cases the values given were found to be significantly different from the ratio of one which Heimburg's hypothesis would predict. Thus these data from Howarth et al. (1968) are consistent with the conclusion that an action potential does emit net positive heat (Table 3). This, again, contradicts Prof. Heimburg's hypothesis that an AP is adiabatic and has no net heat production.

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Table 3. Are the positive and negative heats generated during action potentials equal in absolute magnitude or not? Data from Howarth et al. (1968, taken from their Tables 2 and 3) are analyzed in terms of whether the absolute value of the ratio of negative heat to positive heat production measured during an action potential differs from what is expected if these two heats are equal in absolute magnitude (*i.e.*, if the ratio is expected to be 1.00). A Student's T test (Mendenhall, 1975) was done on these two sets of data. In each case the data supports a conclusion that the absolute value of the ratio of negative heat to positive heat is significantly lower than the expected value of 1.00. Thus (at an alpha level of 0.001), there is justification from these two sets of data to conclude, with high confidence, that the positive heat is indeed greater than the negative heat during an action potential, implying that action potentials do generate net heat.

	Using data from Howarth et al. (1968, their Table 2):	Using data from Howarth et al. (1968, their Table 3):
Sample size (n):	9	25
Mean positive heat observed (μcal/g/impulse) (±standard error of the mean):	6.03 (±0.43)	5.37 (±0.36)
Mean absolute value of ratio of negative to positive heat (paired by cell) (±standard error of the mean ratio):	0.69 (±0.03)*	0.67 (±0.03)
Student's T statistic of mean ratio compared to a value of 1.00:	-10.33	-11.00
Degrees of Freedom:	8	24
Tabular Student's T value at α = 0.001:	-5.041	-3.745

*Note that with pairing the standard error of the mean of the ratio is lower than the standard error of the mean positive heat shown in the row above. This indicates that pairing is appropriate here as it removes much of the random variation found between individual preparations used.

Prof Heimburg (2025, pg. 2) attempts to justify his view that the data presented in the works he cites do not show any AP net heat, where he states... "The integral over the total heat exchange rate is zero within experimental accuracy. No heat is dissipated after the passage of the nerve pulse (Ritchie and Keynes, 1985)." He makes a similar claim in an earlier article (Heimburg, 2021, pg. 33). However, it should be noted that the article Heimburg cites (Ritchie et al., 1985) does state that early methods had poor resolution, and so were unable to resolve the differences, but with regard to more recent measurements they do note that a small rise in temperature is associated with AP firing (Table 1F), and that there is a small positive net heat able to be resolved with more modern methods (Table 1G). Thus, Prof. Heimburg's (2025, pg. 2) comments about "experimental accuracy" may refer to work done before the 1950s, when methods were not able to resolve this small net heat, and would seem to ignore the more recent measurements done with better methods? Indeed, one early set of work, which reported that nerve impulses imposed no temperature change, was done by Hill (1912). But it should be mentioned that in a later review article (Hill, 1959) this same worker noted how inadequate were the methods used in his earlier work, indicated that this issue was important since discovery of net heat would cause the rejection of certain AP hypotheses (such as viewing the AP as an adiabatic wave), and noted that a net temperature change had in fact been convincingly demonstrated when

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adequate methods were later applied to this issue (Table 4A,B,C). In any event, Prof. Heimburg has not presented any statistical analysis of quantitative data to support his claim that when fully integrated across the entire AP there is neither a net temperature or net heat change, and indeed he has not stated just which set of data he means to refer to with regard to his claim that there is no net heat generated by AP firings (Heimburg, 2025). He is, of course, welcome to present the details of such an analysis on identified specific data if he wishes to fill this apparent gap in his argument. But his claim that APs do not generate net heat seems to be contradicted by findings reported in many of the articles he himself cites (Table 1), and also is contradicted by some other articles which he does not cite (Table 4).

Table 4. Statements from articles on the issue of heat production during action potentials.

Statement:	Source:
A.) "If it could be shown that heat really was produced all along a nerve during transmission, then the purely physical theory of conduction would be untenable. A distributed relay system would be required, with energy derived presumably from chemical change."	Hill 1959, pg. 16
B.) "Many things occur in nerve which are quite unlike what happens in the transmission of an ordinary physical wave, while the supposed physicochemical changes were so rapid that they were rather unlikely to go on "reversibly" in such a medium as nerve."	Hill 1959, pg. 17
C.) "As a matter of fact heat is produced, and I had very nearly measured it; for 20 years later the heat per impulse at the same frequency was found to be about 6 X 10^{-8} cal. per gm."	Hill 1959, pg. 17
D.) "... a positive burst of heat of 14 X 10^{-6} cal./gm. occurs in the first 20 msec. after the stimulus, and 12 X 10^{-6} cal./gm. of this is then reabsorbed over the next 100 to 200 msec."	Abbott 1960, pg. 121
E.) "The results are such that it is doubtful if the Joule heat in nerve can in fact be dismissed as completely as at first believed."	Abbott 1960, pg. 123
F.) "In a preliminary account of this work... we favored the possibility that the discharge might involve a process analogous with the melting and splitting of a membrane component, but the fact that the cooling is appreciably more temperature dependent than the spike amplitude, and consideration of the reversibility of the permeability changes in the membrane, now lead us to reject this idea."	Keynes 1968, pg. 224
G.) "It is now clear that in both crustacean (Abbott, Hill & Howarth, 1958) and mammalian (Howarth, Keynes & Ritchie, 1968) non-myelinated fibres there is an initial production of heat during (or soon after) the action potential, 80% of which is rapidly reabsorbed."	Keynes et al. 1970, pg. 29P
Statement:	Source:
H.) "But they also revealed the quite unexpected fact that the true initial heat production is much greater than 2 μcal/g; there is in fact an evolution of about 10 μcal/g, of which about 80% is soon reabsorbed in a phase of negative heat production. The rise of 2 μ℃ observed in the earlier experiments was thus the net temperature rise produced by two opposing phases of heat production."	Ritchie 1973, pg. 151
I.) "In nearly all nerve fibres studies, the negative heat is less than the positive heat, there being a net residual heat of about 2 μcal/g left after each impulse, in excellent agreement with earlier findings: the one exception so far is the olfactory nerve of the pike, where the negative heat exceeds the positive initial heat, leaving the nerve somewhat colder immediately after the spike (Howarth, Keynes, von Muralt and Ritchie, unpublished observations)."	Ritchie 1973, pg. 155

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J.) “What determines the variation in the metabolic cost per impulse from one type of nerve trunk to the next is thus the extent of the ionic movement with each impulse.”	Ritchie 1973, pg. 178
K.) “In all three experiments done at still higher temperatures (16-20℃) the negative heat was only 89±4% of the positive heat.”	Howarth et al. 1975, pg. 361
L.) “The most distinctive feature of our treatment is the proposal that, together with the recharging of the membrane capacitor, the closing of the ion channels explains the heat absorption.”	Margineanu et al. 1977, pg. 3813
M.) “From the peak, the temperature fell relatively quickly and approached a level slightly (10-20% of the peak value) above the base-line.”	Tasaki et al 1992, pg. 808
N,) "... between 50 and 85% of the heat generated during the positive phase was reabsorbed during the negative phase."	Tasaki 1999, pg. 129
O.) “There is thus a direct relationship between the number of Na^+ ions that enter the cell during action potential generation and the energy cost of recovering from the action potential.”	Hasenstaub et al. 2010, pg. 12329
P.) "In fact, much of the brain's energies are used to reverse the ion fluxes that generate APs and synaptic currents."	Yi et al. 2016, pg. 14
Q.) “Based on our study, we identify the release of electrostatic energy by the membrane as the primary mechanism of heat production and absorption by neurons during nervous conduction.”	de Lichtervelde et al. 2020, pg. 1

Turning now to the view under the electrophysiological AP model, with regard to the pattern of heat emission and absorption during an AP, there are two factors considered to be of major influence (Ritchie 1973; Margineanu et al., 1977; Ritchie et al. 1985; Hasenstaub et al., 2010; Yi et al., 2016; Bororg et al., 2020; de Lichtervelde et al., 2020): One factor relates to the capacitance of the membrane, so that with changes in transmembrane potential there is a positive heat generated from the charging of the membrane capacitance, followed by the negative heat generated during its discharging as the membrane potential returns to its resting potential. Another factor is the positive heat generated by the flow of ions down their electrochemical gradient. Both of these processes are thought to be in operation during an AP, so their individual effects sum. The capacitative related shifts in heat are large and symmetrical in absolute magnitude, so in this way through the AP process the capacitative charge of the membrane does return to its initial state. However, the movement of various ions down their electrochemical energy gradients is an irreversible process, resulting in a net change in terms of ion distributions across the membrane which must be much later actively corrected by the cell via pumps and active transport systems, and so this AP related ion flow generates only positive (emitted) heat immediately during an AP, and this is widely thought to be the source of the net heat generated by AP firings (Table 4E,J,O,P). Therefore, the movement of charged items down their energy gradients mandates, by the law of conservation of energy, that heat will be generated. The production of heat by ion flows down their energy gradients is seen even in abiotic systems (Tsutsul et al., 2022), and is seen as accounting for thermogenesis in some other biotic systems as well (Bertholet et al., 2022).

Let us consider more closely how these capacitative events might contribute to the pattern of capacitative-related positive and negative heats produced during an AP. The surface potential of the cytosolic face of the plasma membrane attracts a layer of ions to an extent dependent in part on the difference between the electrical potential of the cytosolic bulk solution relative to that of the surface potential of the inner face of the membrane. Normally the surface potential of the inner face of the plasma membrane is negative relative to the resting potential of the bulk cytosol, and so cations are attracted to the membrane surface. However, during the initial depolarization phase of the action potential, the movement of ions into the bulk cytosolic solution leads to a change in its potential, towards zero and in some cases even to a reversal of its polarity to a positive value. This shift increases the difference between the potential of the bulk cytosol and the surface potential of the inner face of the plasma membrane, which should be expected to result in a stronger relative attraction of cations

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to this surface of the membrane, and so with cations more strongly attracted this may be argued to release heat. This view finds some support in that the altering of the ion gradients across the cell membrane can alter how many Na^+ ions enter the cell during the initial spiking of an AP, this in turn alters the magnitude of the bulk cytosol potential shift observed to occur, and this has been reported to alter the magnitude of the positive heat observed in the initial part of the AP (Howarth et al., 1968). Once we are past the initial depolarization phase of the AP, and enter into the relatively slower repolarization phase, the magnitude of potential difference between the bulk cytosol and the cytosolic face of the plasma membrane lowers. This lowers the potential difference acting to attract cations to the membrane surface from the bulk cytosol, and so cations will tend to move away from the membrane surface, and this may be argued to absorb heat. Thus with the transmembrane potential difference between the bulk cytosol and outside solutions returning to the resting potential at the end of an AP firing the system has emitted and absorbed heat in a reversible manner. This is called the condenser model (Abbott et al., 1958; Abbott, 1960; Keynes, 1968; Howarth, 1975; Ritchie et al., 1985), and it was suggested that if the surface charge density of the cytosolic face of the plasma membrane is high enough, then this might account for much of the heat emitted and absorbed during an AP firing (Howarth et al., 1979; Ritchie et al., 1985), and a recent analysis supports those earlier suggestions (de Lichtervelde et al., 2020). It should be noted that, in the field of material sciences, some capacitative surfaces are shown to be good at storing and discharging energy upon changes in applied electrical field strength (Liu et al., 2025). Electrochemical capacitors have also been shown to produce ionic-based electrical double layers (Greco et al., 2025). In the context of a cell membrane, other sources of reversible heat might include reversible protein conformation changes which are induced by changes in the transmembrane potential during an AP (Table 4L) (Murugan et al., 2004; Crotty et al., 2006). Or, perhaps, the changes in transmembrane potential may induce an alteration of the surface charges displayed at the inner surface of the plasma membrane, which would be consistent with the earlier noted reports of a change in capacitance of the membrane during an AP.

Returning to the transmembrane current-related heat, it seems that some of the advocates for the soliton-AP model deny that during an AP there is any net transmembrane ion flow occurring at all, and they also refute a role for voltage-sensitive protein-based ion channels which would alter the permeability of the plasma membrane to allow for such specific ion flows during APs (Appali et al., 2012; Gonzalez-Perez et al., 2014; Heimburg, 2010; Vargas et al., 2011). Apparently from their perspective, such processes and events would inevitably result in net heat generation. The production of net heat would then refute the proposal made by the soliton-AP model that an AP is a type of physical wave and so should be adiabatic and produce no net heat. Indeed, it has been noted by earlier researchers that the finding of net heat being produced by an AP lead to their rejection of proposals that the AP might be a wave or other adiabatic process (Table 4A,F). Therefore, here we see that some supporters of the soliton-AP model seem to be quite willing to propose that this entire area of evidence for net transmembrane ion flows during an AP leading to net heat generation should be set aside, as it contradicts their soliton-AP model, which they claim to be mandated by thermodynamic principles. Thus, they argue that we should reject the evidence that there is any transmembrane ion flows during an AP, and so in that way no heat would be generated, in their view. They have not offered any actual evidence that there is no transmembrane ion flows during an AP. Instead, they use their model to judge the data, and only data consistent with their model are accepted by them.

Of course, there is much evidence for the flow of ions across the membrane during AP firings, obtained by various methods and well reviewed in the published literature; the following are just a few such published works (Hodgkin et al., 1939; Keynes, 1951; Hodgkin et al., 1949a, 1952b,c,d,e, 1955; Abbott et al., 1958; Cole et al., 1960; Tasaki et al., 1948, 1962; Keynes et al., 1965; Howarth et al., 1968; Shepherd, 1988a; Thiel et al., 1997; Johnson et al., 2002; Bezanilla, 2006; Bean, 2007; Beilby, 2007; Powell et al., 2021). It may be noted that Heimburg (2025) does himself cite several items which present evidence of transmembrane ion flows during APs, so while he apparently is well aware of this evidence he seems to choose to just ignore such findings and their implications, and does not

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comment upon them. The changes in membrane ion permeability and transmembrane ion flows during APs have been confirmed so many times by various methods, and the high energy flow through nervous tissue operation is so well known (Attwell et al., 2001), that it seems startling to consider that such solid highly reproduced evidence can be proposed to be wrong based on the mere unconfirmed assumptions of the soliton-AP model. But this illustrates, yet again, how many of the advocates of the soliton-AP model consider only evidence that supports their model to be valid.

What should we conclude

If the good people who advocate for the soliton-AP model would present actual evidence, from actual measurements, that during AP firings there is indeed no detectable net heat generated, then their arguments would be stronger. But they present no such evidence. This is very odd, as our good Prof. Heimburg is, himself, a talented lipid biophysicist with much experience in the measurement of heat by various methods. He would seem to be well placed to make such measurements about heat production during APs, but, twenty years after publishing his soliton-AP model, he still offers no actual evidence in support of his claim that APs are adiabatic. Instead of offering findings from new measurements, he (Heimburg, 2025), incorrectly and inaccurately, claims that the findings of Abbott et al. (1958) supports his view that APs are adiabatic, when in fact Abbot et al. (1958) clearly state that they found that there IS net positive heat generated from an AP (Table 1A). Further, Heimburg's claims (Heimburg, 2021, 2025) that the condenser model can not account for some of the heat changes seen during the pattern of positive and negative heat during AP firing. His claims are presented without any comments made at all on the views presented by others who suggest that this condenser model can indeed account for part of this pattern of heat (Howarth et al., 1979; Ritchie et al., 1985; de Lichtervelde et al., 2020). Add to this the rejection of the reports of observation of heat generated from transmembrane ion flows during APs (Tables 1 and 4), which is supported by statistical analysis of some of the presented data (Tables 2 and 3), as well as his rejection of ions moving down their energy gradients during APs as that would generate heat, and one is hard pressed not to adopt the notion that the view which some of the advocates of the soliton-AP model take is indeed one in which they choose to actively ignore alternatives that do not fit with their model. Their denial of the reproducible reports of net heat generation by AP firings is all the more odd as the good people who advocate for the soliton-AP model often claim justification from thermodynamics (i.e., the study of heat) as a major argument for why their model should be accepted. Yet, as of now, they have not reported measurements of the heat of an AP which would support their claims. Instead they seem to be telling us what their model would predict, and given their high confidence in their soliton-AP model, they apparently feel that all reports of net heat from an AP must be in error.

Thus, there is no clear or compelling evidence presented to force us to reject the reports that APs do generate net heat; indeed the published evidence overwhelmingly supports the conclusion that AP firings do generate net positive heat. This conclusion may, of course, be altered with new information. But, as scientists we must demand actual evidence in support of this claim that APs are adiabatic before accepting it. So in the absence of compelling evidence, there can be no acceptance of this claim, that the AP generates no net heat and is adiabatic in its operation, at least not at this time. This obviously has implications for the viability of the soliton-AP model, which describes the AP as being an adiabatic wave-like process. How, after all, can an adiabatic wave account for the net heat reported to be generated by AP firings?

In Conclusion: On Standards of Evidence and the Dangers of Abandoning the Scientific Method

As noted earlier (Meissner, 2018, 2022), under the soliton-AP model, Heimburg and some others often make claims which seem to contradict well established findings or which ignore reasonable alternatives which would be consistent with the well accepted electrophysiological AP model, and they also often fail to support their claims with clear evidence. This lack of evidence, ignoring of evidence, and even skewing or misrepresentation of evidence in some cases, has caused a rather

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strong reaction amongst neurobiologists (Fox, 2018), and is quite likely a large part of the reason, rather than an unwillingness to consider new models as some suggest (Drukarch et al., 2025) or a lack of appreciation of wave-like phenomena as others suggest (Shrivastava, 2021), for why this soliton-AP model has failed to gather acceptance in the broad scientific community. To emphasize this point, let us review a few examples already mentioned above.

For instance, as noted above, the claim is made that APs have no net heat, when the consensus view (Tables 1, 4), based on reproducible measurements, is that APs do generate net heat. The claim is also made that during an AP no net transmembrane ion flow occurs, as that would generate net heat, even though there are many accepted and well replicated reports of transmembrane ion flows during APs. Also, as noted earlier in this article, it is quite possible that anaesthetic effects occur because of their interactions with proteins, rather than through the inhibition of a lipid phase transition; compelling evidence for a lipid phase transition during an AP not having yet been reported, whereas anesthetic inhibition of many protein activities needed for AP firing under the electrophysiological AP model having been reported. In addition, under the soliton-AP model the claim is made that the apparent widening of the plasma membrane during an AP, and changes in its optical features, may be due to a lipid phase transition, but this ignores the alternate view that voltage-dependent changes in membrane protein conformations may also account for this apparent membrane widening and changes in optical features (Meissner, 2018). And the claim that the soliton-AP is said to be adiabatic, coupled with the claim of AP passage upon collision, was noted above to imply a possible violation of the law of conservation of energy.

The above claims, and many others, are apparently made as these are what the soliton-AP model advocates feel is implied by their model, and they apparently have such high confidence in their model that they feel there is no need on their part to produce actual evidence for these claims. Instead they merely argue that each of the sets of evidence which contradicts their model are somehow wrong (exact details of how they are wrong are typically not presented), and imply that any alternate explanation for the phenomena they explore which might be consistent with the electrophysiological AP model should be ignored, simply because it is inconsistent with their model. This is seen where Heimburg (2022b, pg. 26) discounts any attempt to account for AP features via ion channels or other molecular events where he states: “Therefore, any molecular attempt to understand the dependence of a macroscopic biological system on temperature, pressure, voltage or drugs must necessarily be incomplete and will most likely be wrong.” Heimburg’s position that descriptions at the “molecular” level are unacceptable seems rather odd when it is recalled that his soliton-AP model makes use of a lipid phase transition, which is itself a description of events at a molecular level, and so constitutes a molecular mechanism, one which Heimburg et al. (2005) relates to temperature, pressure, voltage, and interactions with drugs. Perhaps this suggests that molecular mechanisms which are consistent with Heimburg’s views are acceptable, such as a lipid phase transition, and the reason for rejection of other molecular mechanisms is merely that they are not consistent with Heimburg’s favored model? It would help if our good Prof. Heimburg and others would tell us why this molecular mechanism of a lipid phase transition should be seen as acceptable, but that other molecular mechanisms should be all swept aside without consideration of their details? In this way it seems that these good people are using a very different standard of evidence compared to that which most scientists use. Without solid data in favor of the soliton-AP model, and without clear statements of what is “wrong” with the current electrophysiological AP model, these claims often produce an impression of being highly subjective and biased. This is perhaps a major reason for this model’s failure to gain support.

Thus, it seems that what some of the advocates of the soliton-AP model are using as a standard of evidence is one that is not consistent with that used in your grandparents’ scientific method. Rather the advocates of the soliton-AP model are apparently using a standard of evidence which is consistent with that used by your great, great, great, etc... grandparents, which was a metaphysical/natural philosophy approach to examining the universe, used long before the scientific method was even devised. Aspects of this different approach have been described previously (Meissner, 2022). Under

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this metaphysical approach, a model is devised which is argued to be consistent with eternal and well established rules, principles and laws. Thus the relation of the model to those rules is argued to establish it's credibility in the minds of its advocates, and actual evidence for or against the model is not then their central concern. Once such a model is generated, then examples of specific data which may support it are sought in a classical inductionist manner, and any sets of evidence which contradicts the model are argued against (Meissner, 2022). Thus the model is used to judge which sets of evidence are acceptable, and which are to be rejected. Therefore, in the above examples, the AP is argued to have no net heat, and to have no net transmembrane ion flow, not because of any new or compelling evidence that is being brought forward to support such claims, but because that is the view consistent with the model these good people are convinced must be correct. Their confidence, belief, or faith if you like, in their model is centered on its connection to the eternal associated laws and rules, and is not based on any preponderance of evidence.

This approach of referring to eternal laws also seems to lead advocates for the solition-AP model to argue against the use of an empirical approach. This is seen where Heimburg dismisses the work of Hodgkin et al. (1952a) where he states (Heimburg 2022b, pg. 11): "... the description of the action potential is a fit to the experimental data rather than a theory based on first principles." It should be noted that the electrophysiological AP model has a basis in terms of the laws of conservation of energy and of charge, and as mentioned earlier to other physical principles. Surely, these conservation laws are "first principles"? Exactly which "first principles" Heimburg (2022b) means to refer to is left unclear, but obviously the electrophysiological AP model has strong connections to "first principles" but Heimburg seems to discount such connects. Again, what Heimburg is suggesting here seems to be a very different standard of evidence from that used under the scientific method. Thus he attacks the electrophysiological AP model's relationship with first principles, rather than being concerned with evidence which may support it. Thus the belief is in the connection to the eternal principles, not in the actual collected data. This faith-based metaphysical view extends further to allow for events for which no actual evidence has been put forward, and to allow for the discounting of other alternative explanations of certain phenomena even when evidence for them exists.

Thus, twenty years after its introduction, the fact that the soliton-AP model has not yet produced a compelling set of evidence for a major lipid phase transition happening during an AP does not seem to trouble many of the advocates of this model at all. Nor are they concerned by the notion that the changes in surface potentials they claim would occur during such a hypothetical lipid phase transition have not been shown to have macroscopic effects, and so have not been shown to be able to account for the pattern of electrical changes we see during an AP (Meissner, 2022). They know what is expected under their model, and finding evidence for these sorts of specific features is seen as just a trivial detail, or perhaps argued to be evidence not yet obtained due to technical difficulties in finding the evidence they are confident should be out there in support of their model. Instead their belief that thermodynamics or some other fundamental physical law, somehow, mandates that their model must operate dominates their views, and the notion of describing an AP based on specific molecular events other than their own mechanism of a lipid phase transition is rejected. Under this view all evidence contrary to their soliton-AP model is discounted, and also the lack of positive supporting evidence is not seen by these advocates as a reason to abandon their model, as they are not primarily making an evidence-based argument.

All of this is, of course, very different from the standard of evidence used under the scientific method. This apparent abandonment of the scientific method by some of the advocates of the soliton-AP model may thus be a major reason for why their model has failed to gain acceptance in the broader scientific community. As, under the scientific method, any proposed model which lacks compelling evidence for its proposed explanation of phenomena, or which fails to clearly account for existing evidence which conflicts with the proposed model, or which fails to show how reasonable alternative explanations may be discounted, is unlikely to gain much support. The scientific method uses an evidence-based approach in which the new evidence judges the model, while many of the advocates

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of the soliton-AP model are presenting a faith-based metaphysical approach in which evidence is not the critical feature, rather their model is used to judge the evidence (Meissner, 2022).

This metaphysical natural philosophy-based standard of evidence which some of the advocates for the soliton-AP model have adopted calls upon scientists to judge their proposed model not by the evidence, but by its relationship to higher laws, or in terms of the beauty of its equations, or due to the reputations of past important scientists who may have stated speculations which happen to be consistent with the soliton-AP model. This, obviously, is a rather difficult standard of evidence for many scientists to accept. But it implies, perhaps, that we should not view some of the advocates of the soliton-AP model as being scientists who use the scientific method. If they were such, they would be doing the necessary tests and judging their model by the new evidence gathered. Rather, it might be more accurate to view some of the advocates of the soliton-AP model as being natural philosophers who are putting forward metaphysics and who make use of inductive reasoning to "cherry pick" what evidence fits to the model they believe to be valid? Thus the model judging the data seems perfectly natural to them, though it shows a complete abandonment of the scientific method.

Thus, twenty years after its introduction, the soliton-AP model is still not well accepted by the broad scientific community. And that state is unlikely to change so long as many of the advocates of this model are not really attempting to find new evidence to either support their model or to refute that which upholds the modern electrophysiological AP model and its interpretation of many of the phenomena associated with AP firings. Even something as fundamental for the soliton-AP model as demonstrating that during an AP there is a major lipid phase transition happening has not been shown, yet, by the advocates of the soliton-AP model to have solid evidence in support of this basic assumption of their model. Those who advocate for the soliton-AP model are welcome, of course to carry out tests which, if certain results are obtained and found to be reproducible, might help them to garner support for their model amongst the scientific community. Many such tests have been suggested (Meissner, 2018, 2022), but by and large these tests have not, as of this date, had their results reported in the literature. Only if they give actual evidence so that, under the scientific method, their model may be judged as being supported by new evidence would the soliton-AP model be acceptable to scientists who work under the scientific method. For the advocates of the soliton-AP model to expect scientists to stop using the scientific method, or to ask scientists to reject well replicated findings which conflict with the soliton-AP model simply on faith because their model has some sort of association with an eternal law, is in effect asking scientists to stop being scientists - it is asking too much. This, it is argued, is one of the main reasons for the lack of acceptance seen for the soliton-AP model among the scientific community.

New styles of thinking are always welcome. But they should be subjected to rigorous evaluation under normal standards of evidence. When the standards of evidence are altered to fit the model, that can risk undermining science (Plait, 2023; Erduran, 2025). Thus, there is a danger in the apparent abandonment of the scientific method by some of the advocates of the soliton-AP model. Consider; there are in our society today many groups who have a favored idea by which they judge all data, and in regard to which certain data are accepted and other data are rejected. One example of such a group might be the "intelligent design" advocates who promote creationist views and reject biological evolution theory (Behe, 1996). The scientific method (Blystone et al., 2006), by demanding that views be verified by the production of new evidence, is extremely different from how such groups judge the data by their favored model. Thus, by their apparent rejection of the scientific method, some of the advocates for the soliton-AP model may, perhaps, not only have stopped being scientists themselves and become natural philosophers, but their promotion of new standards of evidence may well constitute an attack upon the very standards of evidence which underpin the scientific method and so establishes the authority of modern science. This should be a cause of concern to all scientists who wish to uphold proper standards of evidence as used under the scientific method. By using a very different standard of evidence some of the proponents of the soliton-AP model may well be threatening the authority of science.

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That said, the advocates of the soliton-AP model are free to seek for positive evidence for their model, evidence which, under the scientific method, might be taken as compelling acceptance of the assumptions and predictions associated with their model. If they can achieve that, then their proposed model may well be taken up by more scientists as a viable accounting of the AP. On the other hand, if such supportive evidence can not be obtained, meaning that reasonable tests refute their model's assumptions or predictions, then, the good people who advocate for the soliton-AP model should accept that their model is just not supported by compelling evidence and either adjust their model so that it conforms with well accepted data or give it up entirely. But the philosophical approach they have adopted seems to preclude their acceptance of the results of such tests. And so we might expect in another twenty years time to find some of these people still putting forward a fundamentally metaphysical view without solid evidence.

One other issue seems to need mentioning: That of how some advocates of the soliton-AP model, when putting forward their arguments also display a rather unfortunate tendency, noted in this article and previously (Meissner, 2022), to cite articles in support of their claims, when in fact the cited articles present findings which either directly contradicts the claims made by the advocates of the soliton-AP model or concludes something other than what is claimed. As noted above, this tendency is seen in the claim by Heimburg (2025) that the work of Johnson et al. (1950), which examined anaesthetic effects on a protein, instead showed effects on membrane lipids. Also, where the Kim et al. (2007) article found vertical displacement on AP arrival in a structure in the nervous system, Heimburg (2025) then incorrectly attributed this finding to a longitudinal displacement. Furthermore, and perhaps most important, the continuing claim by Heimburg (2021, 2025) that the Abbott et al. (1958) article supports a conclusion that AP firings do not emit any net heat, when in fact Abbott et al. (1958) conclude that net heat is emitted from AP firings (Table 1A). These and other unjustified mischaracterizations, some mentioned previously (Meissner, 2022) and others not mentioned, of the findings reported in various articles does nothing to advance the arguments put forward by the advocates for the soliton-AP model, rather it acts largely to undermine the credibility of these good people in the eyes of the broader scientific community. Speculation is one thing, making unsupported initial claims as part of presenting a new model is typical, but to make claims contradicted by the immediately cited literature is neither a productive nor honest approach.

Therefore, I would, again (Meissner, 2022), urge the good people who advocate for the soliton-AP model to use the scientific method and collect new data from new measurements and then judge their model by the data, as this is the highly productive approach which has been taken by most modern scientists in their studies. If those new data support their model, then their model may have some chance of gaining support, but if those new data are not consistent with their model, then they should question their model's validity. That is the standard of evidence used under the scientific method, and no other approach is likely to be accepted widely by scientists.

In closing, with regard to Heimburg's (2007, pg. 285) "courageous" assumption that events in non-living artificial lipid bilayers should be assumed to occur in a similar manner in the more complex biological membranes of living organisms, the following quote (Asimov, 1992, pg. 73) might be appropriate:

> *"Nevertheless, scientists are human, and in science, as in other facets of human thought, an assumption that has been held long enough takes on the force of cosmic law. People forget that it is only an assumption and find it difficult to consider the possibility that it might be wrong."*

Acknowledgments: The author wishes to thank the good folks at several of the University of the Philippines campuses, including most recently at the Institute of Biology, UP Diliman, for allowing a retired professor, and former Cornell University janitor, to at least offer assistance as a volunteer on each of their campuses. Thanks is also due to many people who at various times over several years have patiently replied to e-mails containing questions on a variety of topics related to this article, including most recently Prof. Thomas Heimburg.

Conflicts of Interest: The author (STM) declares no conflicts of interest.

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